MODIFIED STEROIDS

RESUME

THESIS SUBMITTED FOR THE DEGREE OF

Doctor of Philosophy

IN

CHEMISTRY

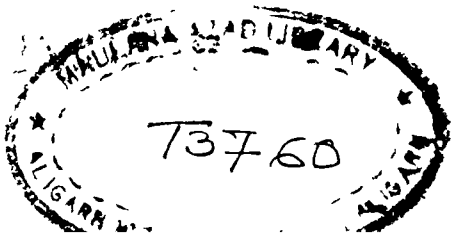
TO

The Aligarh Muslim University, Aligarh

BY

MD. ANJUM REYAZ KHAN

DEPARTMENT OF CHEMISTRY
ALIGARH MUSLIM UNIVERSITY
ALIGARH (INDIA)
1988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PART - I(A)

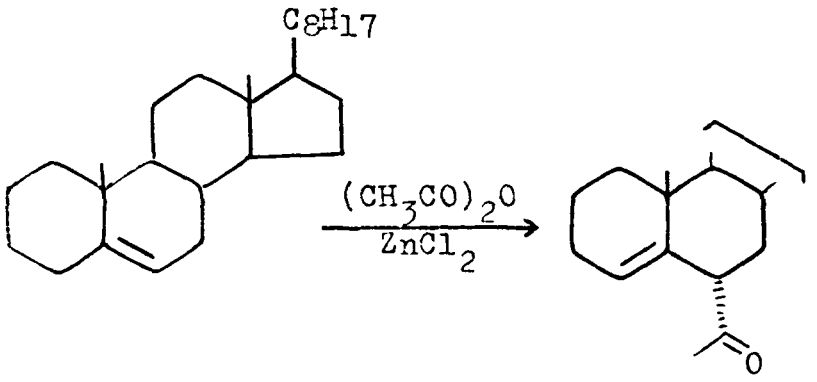
REACTION OF STEROIDAL OLEFINS WITH ACID ANHYDRIDES AND ZINC CHLORIDE

In the recent past much attention has been paid towards the acylation of cyclic and acyclic olefins with acid anhydrides and zinc chloride. The acylation of olefins leads to the formation of β,γ-unsaturated ketones. A survey of literature reveales that no significant work on acylation of steroidal olefins with acid anhydrides and zinc chloride has been reported.

The present work is concerned with the synthesis of β,γ-unsatureted ketones in the cholestane series. Steroidal olefins chosen for the present exploratory studies are cholest-5-ene (I), 3β-chlorocholest-5-ene (IX) and 3β-acetoxycholest-5-ene (X). In addition to these olefins, cholest-5-en-3-one (XII) has also been included in the present study. The acylation in all cases has been carried out by acetic anhydride and propionic anhydride in the presence of zinc chloride. The products obtained have been characterized on the basis of their spectral properties, chemical transformation and comparison with the authentic samples where available.

The systems studied however, donot seem to give consistent results as was expected. Needless to say, that variations in results may be due to a number of factors and further work in this area may eventually be required.

In the following flowsheet, the results have been summarized. Probable pathways for variousstransformations have been suggested.



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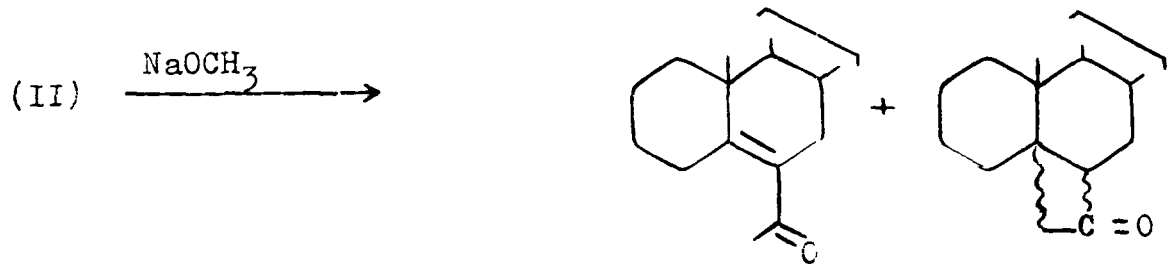

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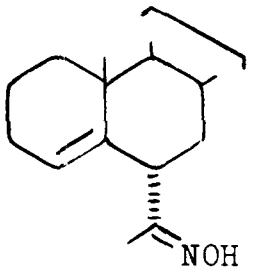
(II) —Oximation→ 

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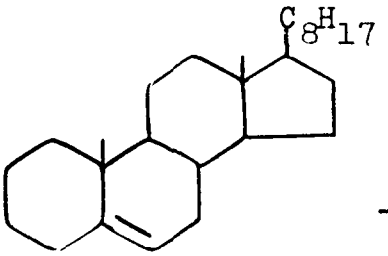
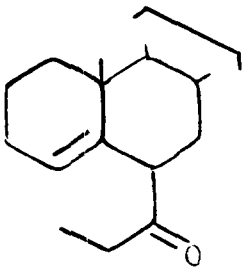


(I) —$(C_2H_5CO)_2O$, $ZnCl_2$→ 

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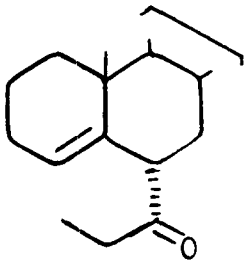
(VI) —$NaOCH_3$→ 

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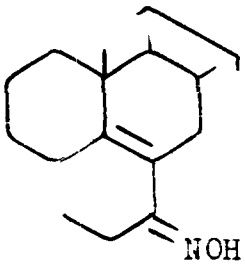
(VI) —Oximation→ 

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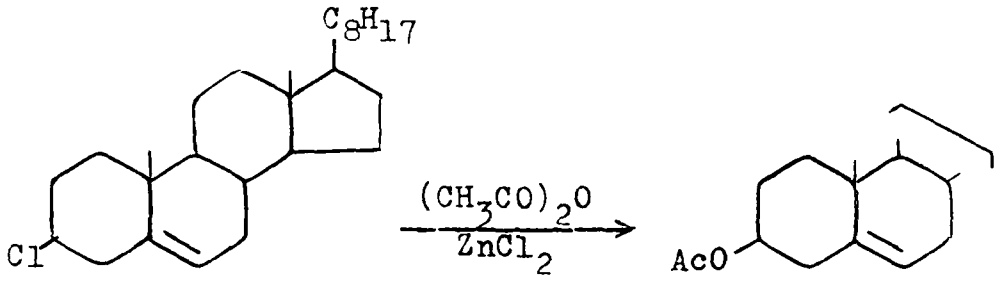

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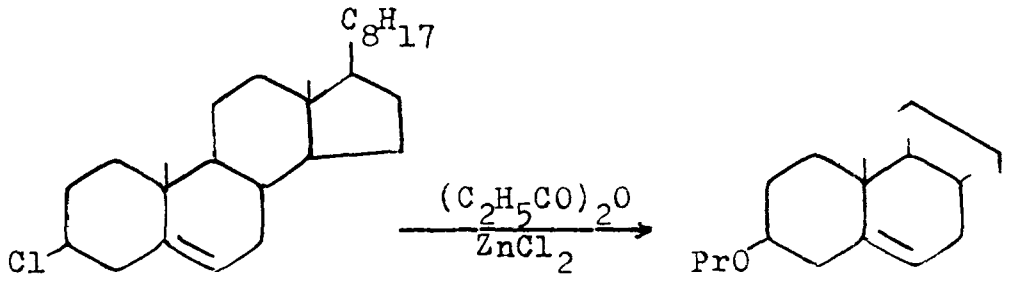

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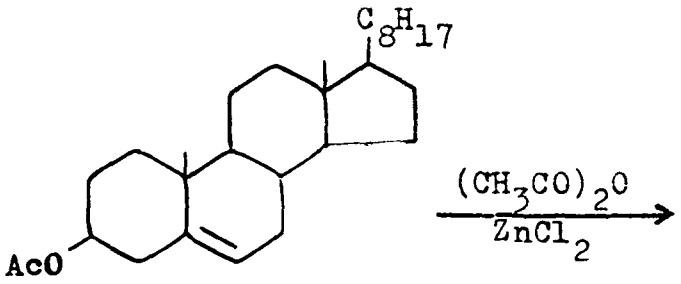

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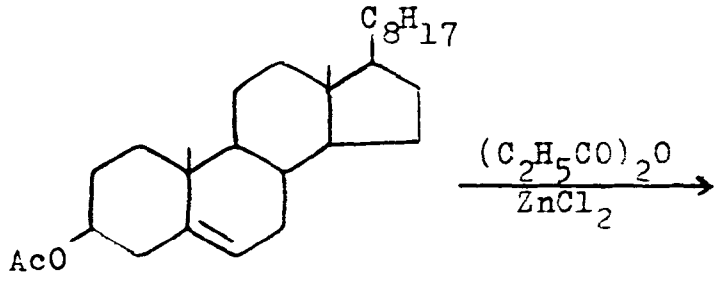

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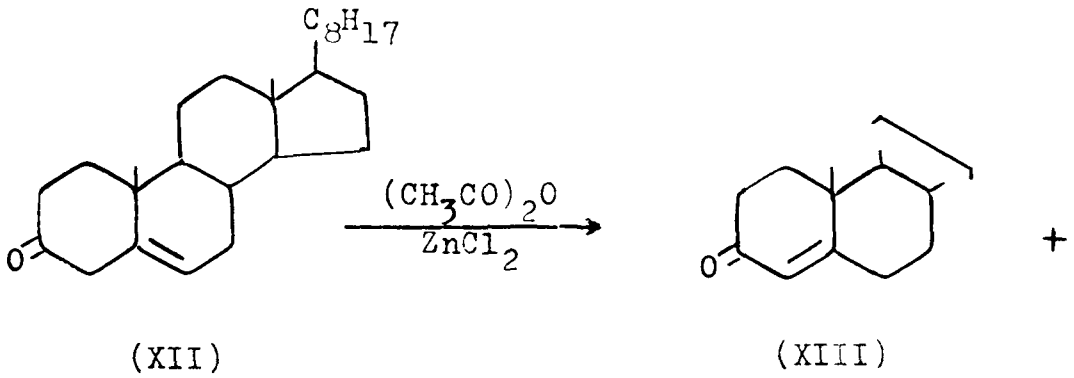

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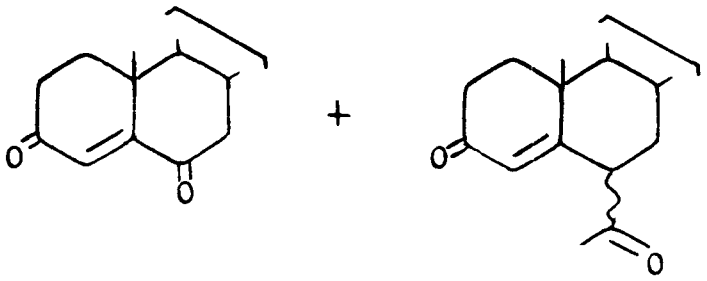
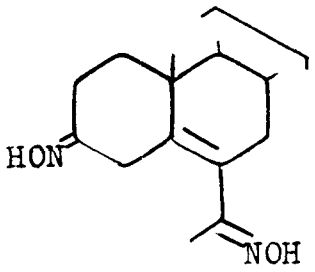


(XIV) (XV)

(XV) Oximation



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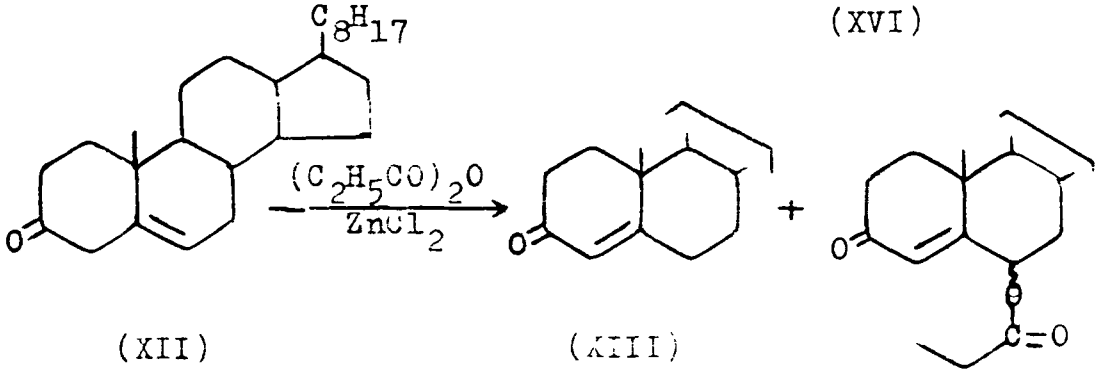


(XII) (XIII)

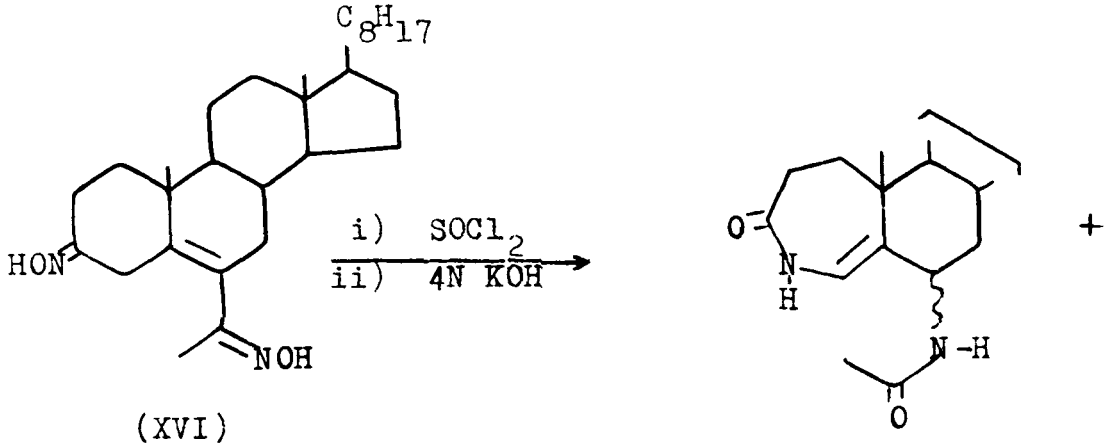
(XVII)

PART - I(B)

AZASTEROIDS

Previous work from our laboratory has described the Beckmann rearrangement and the Schmidt reaction of several steroidal ketoximes and ketones, respectively in order to prepare azasteroids with possible biological potential. The work was mainly concerned with the cholestane and stigmastane series and as a consequence a large number of the then unknown azastreoids were synthesized.

As an extension of the above work, steroidal ketones, suchas, 6ξ-acetylcholest-4-en-3-one (XV) and 2,6-dibromocholest-1,4,6-trien-3-one (XXI) and ketoxime, 6-acetylcholest-5-en-3-one-1',3-dioxime (XVI) were subjected to the Schmidt reaction and the Beckmann rearrangement, respectively, in order to prepare hitherto unsynthesized azasteroids. The characterization of the products thus obtained was done on the basis of their elemental analysis and spectral properties.



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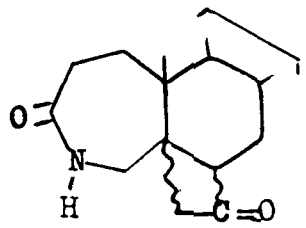

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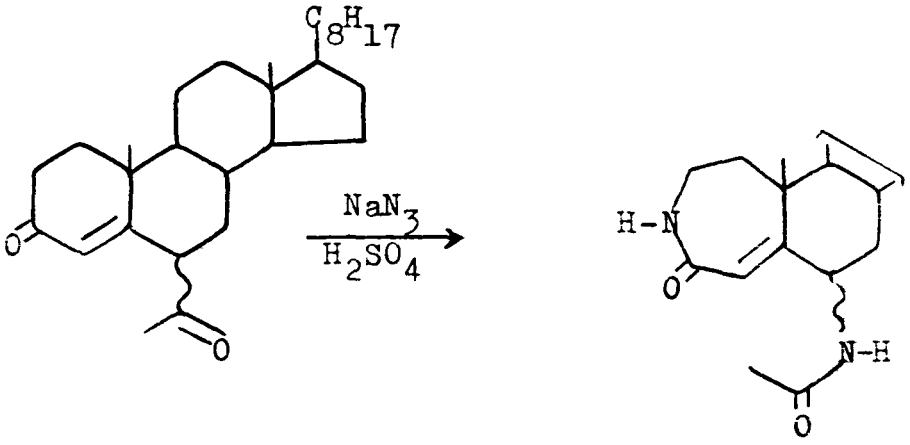

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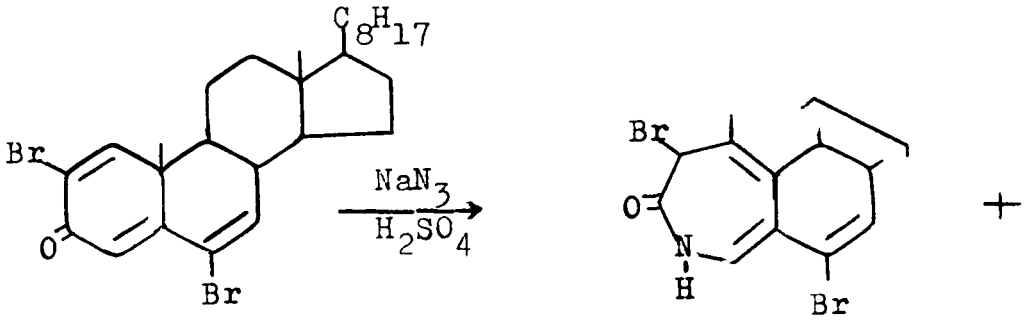

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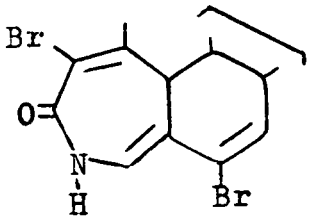


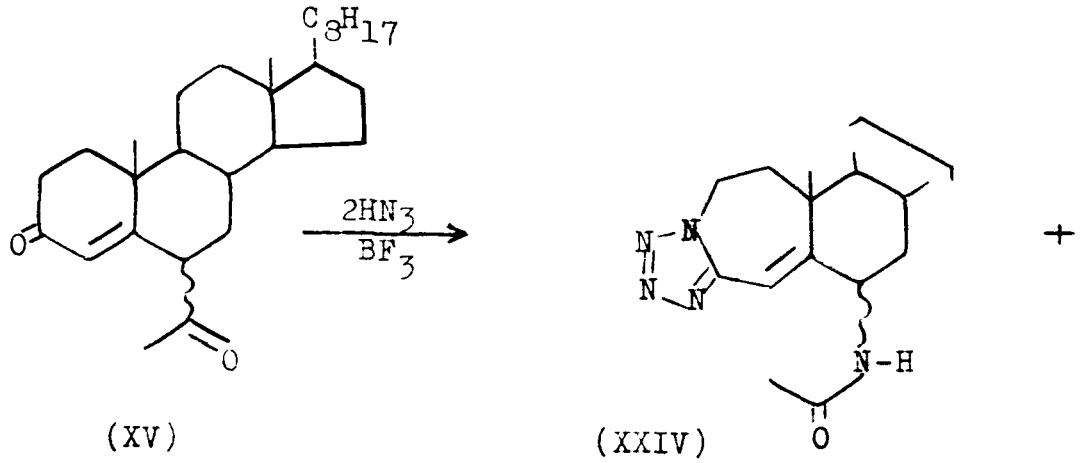
(XXIII)

PART - II

TETRAZOLOSTEROIDS

In recent years much attention has been paid towards the formation of steroidal tetrazoles because of the significant biological properties associated with a number of tetrazoles and their use as potential drugs. As a result of this several papers describing the synthesis of tetrazoles from various steroidal ketones have appeared from our laboratory also.

This chapter is an extension of the above work on the synthesis of tetrazoles from the cholestane series. It describes the reaction of the steroidal ketones, 6ξ-acetyl-cholest-4-en-3-one (XV) and seco-ketoesters like methyl 5-keto-5,6-secocholestan-6-oate (XXVI) and methyl 5-keto-5,6-secocholest-3-en-6-oate (XXVIII) with an excess of hydrazoic acid in the presence of boron trifluoride as the catalyst. The products obtained from the above reactions have been characterized on the basis of their elemental analysis and spectral properties.



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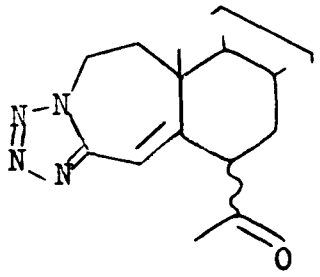

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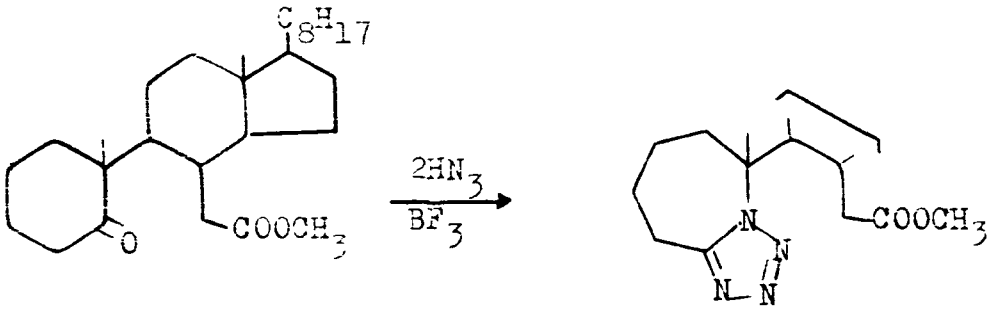

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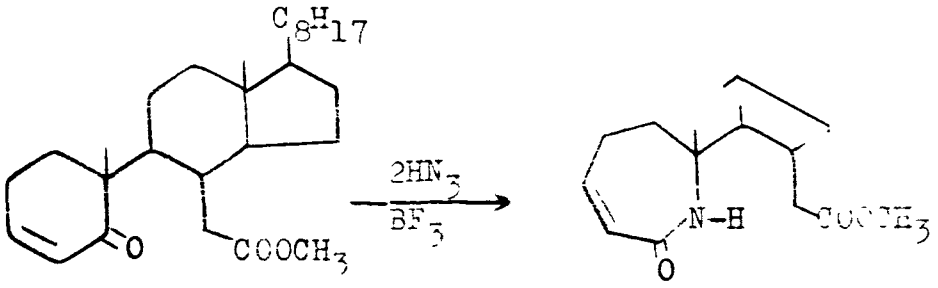


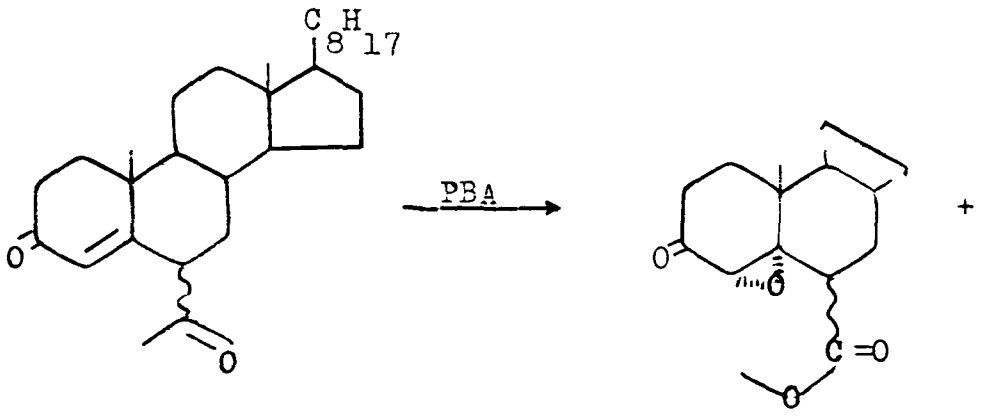
(XXVIII) (XXIX)

PART - III

OXASTEROIDS

Previous work from our laboratory had described the Baeyer-Villiger oxidation of several ketones in order to prepare oxasteroids. The work was mainly concerned with the cholestane and the stigmastane series and as a result, a large number of the then unknown oxasteroids were synthesized.

As an extension of the above work steroidal ketones, suchas 6ξ-acetylcholest-4-en-3-one (XV) and 2,6-dibromo-cholesta-1,4,6-trien-3-one (XXI) were subjected to the Baeyer-Villiger oxidation in order to get the corresponding oxasteroids. The characterization of the products thus obtained was done on the basis of their elemental analysis and spectral properties.



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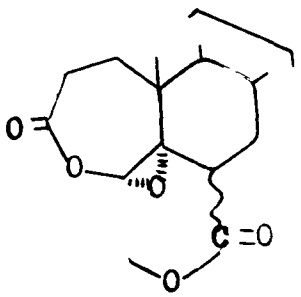

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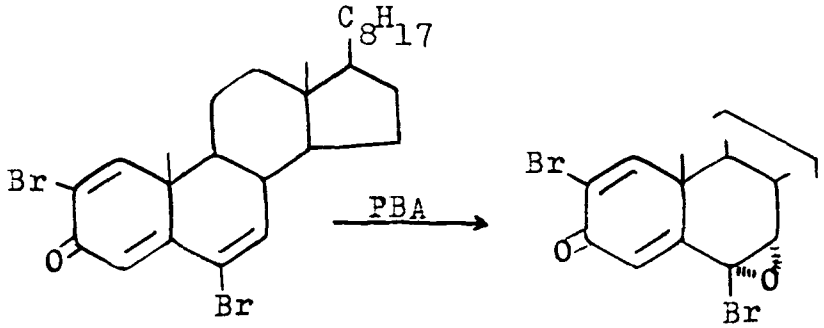


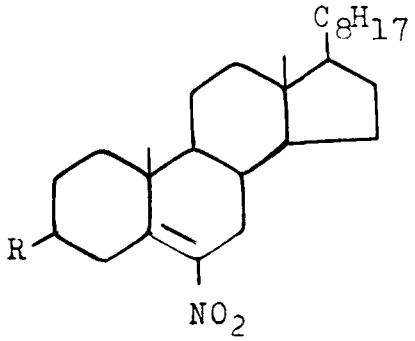
(XXI) (XXXII)

PART - IV

MASS SPECTRAL STUDIES ON STEROIDAL NITROOLEFINS

During the last twenty five years or so the mass spectrometry has developed to become a very powerful analytical tool in the characterization of organic compounds. Virtually, every class of organic compounds had been subjected to this study and useful structure-spectra relationships have been established. It was, however, found that no significant studies have been made on the mass spectrometry of steroidal nitro compounds and this prompted as to undertake such studies

on some of the structurally related steroidal nitro compounds. These included the steroidal nitroolefins suchas 6-nitrocholest-5-ene (XXXIII), 3β-chloro-6-nitrocholest-5-ene (XXXIV) and 3β-acetoxy-6-nitrocholest-5-ene (XXXV).



(XXXIII) R, H
(XXXIV) R, Cl
(XXXV) R, OAc

The proposed fragmentation pathways are supported in some cases by appropriate metastable peaks. The mechanisms suggested are only tentative in the absence of appropriate deuterated analogues and the accurate mass measurements.

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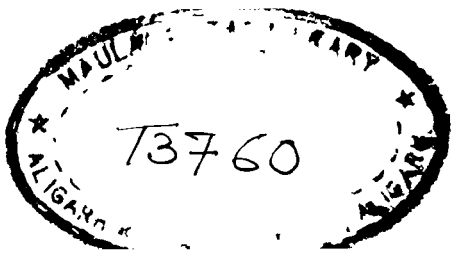

Dr. M. S. Ahmad
M. Sc., Ph. D. (Manchester)
Professor of Chemistry

Aligarh Muslim University
Department of Chemistry
ALIGARH-202001 INDIA

Dated ....16.8.1988..

This is to certify that the work embodied in this thesis entitled, "Modified Steroids" is the original work of Mr. Md. Anjum Reyaz Khan accomplished under my supervision. The thesis is suitable for the submission for the award of the degree of Doctor of Philosophy in Chemistry.

M. S. Ahmad

(M.S. Ahmad)

ACKNOWLEDGEMENT

I wish to express my heart felt sense of gratitude to Prof. M. Shahabuddin Ahmad for his constant help, unabated interest, encouragements and all possible facilities during the work. It is due to his constructive criticism and zealous efforts that the present work has taken presentable shape. Thanks are also due to Prof. W. Rehman, Pro-Vice Chancellor, A.M.U., Ex-Chairman Department of Chemistry and Prof. S.M. Osman, Chairman Department of Chemistry for providing necessary facilities.

I would like to make a thankful note of Dr. M. Mushfiq and Dr. S.K. Raza who have always been of great help throughout the project. My colleagues deserve a great many thanks for they stood by me at difficult times. The execution of the uphill task of typing the script by Mr. Mohd. Zubair Siddiqui is gratefully acknowledged.

I am grateful to the Concil of Scientific and Industrial Research, New Delhi, for financial assistance.

(Md. Anjum Reyaz Khan)

CONTENTS

SUMMARY

PART - I(A)

REACTION OF STEROIDAL OLEFINS WITH ACID ANHYDRIDES AND ZINC CHLORIDE

In the recent past much attention has been paid towards the acylation of cyclic and acyclic olefins with acid anhydrides and zinc chloride. The acylation of olefins leads to the formation of β,γ-unsaturated ketones. A survey of literature reveales that no significant work on acylation of steroidal olefins with acid anhydrides and zinc chloride has been reported.

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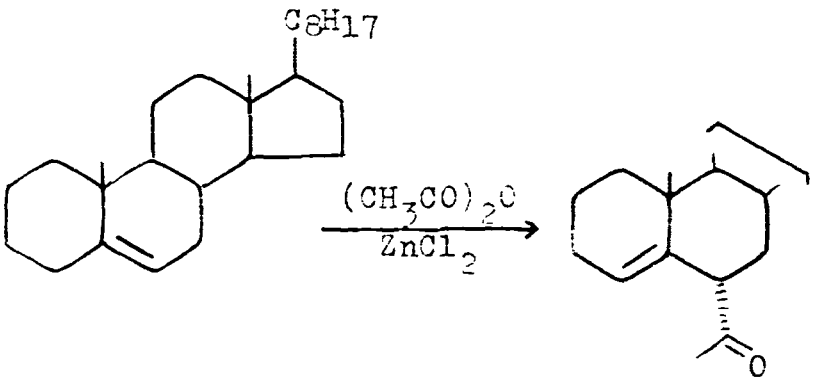

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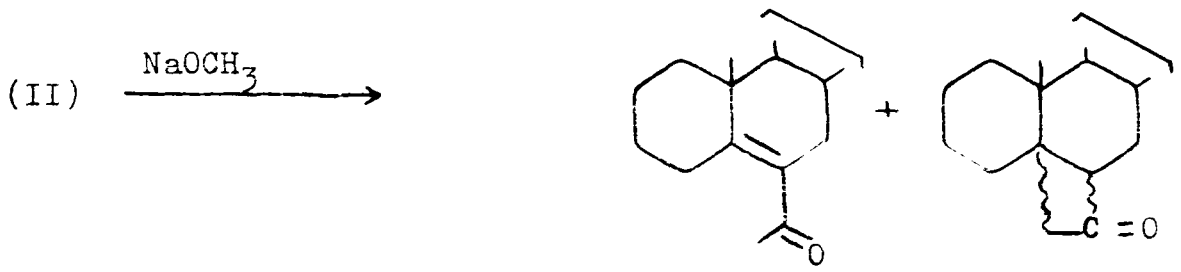

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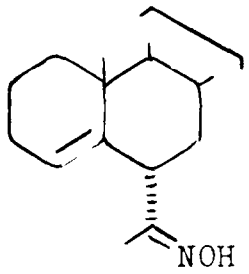
(II) —Oximation→ 

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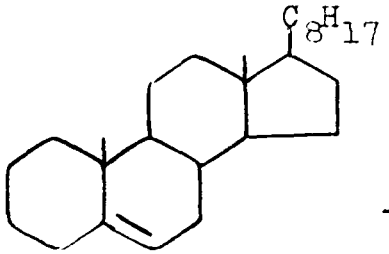
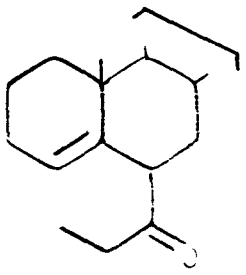


(I) —$(C_2H_5CO)_2O$, $ZnCl_2$→ 

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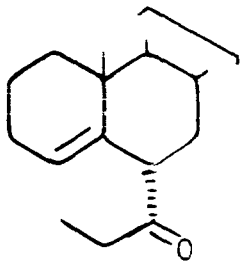
(VI) —$NaOCH_3$→ 

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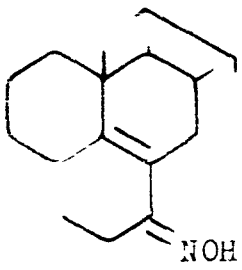
(VI) —Oximation→ 

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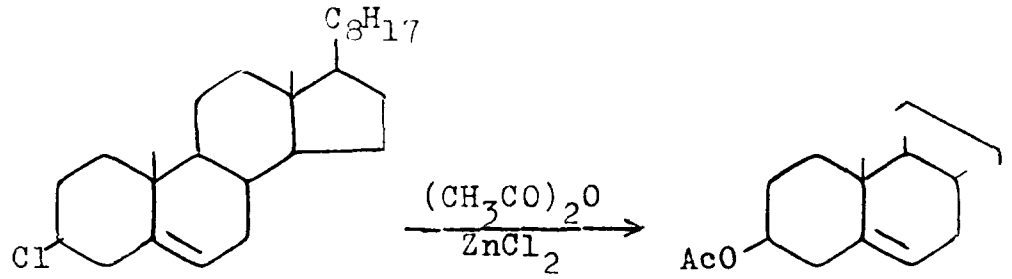
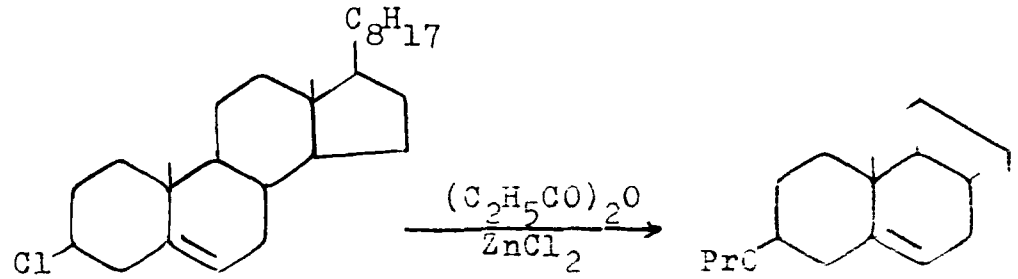
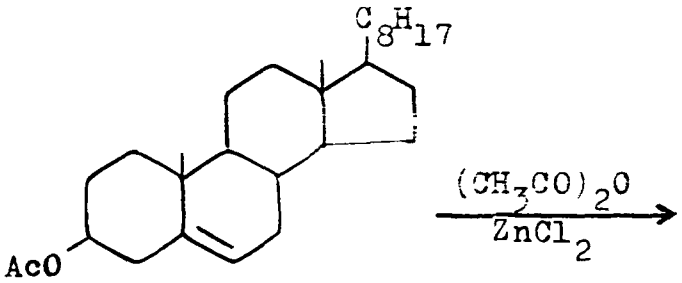


(IX) (X)

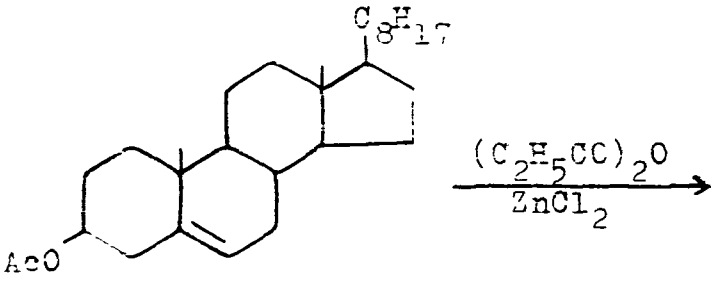


(IX) (XI)



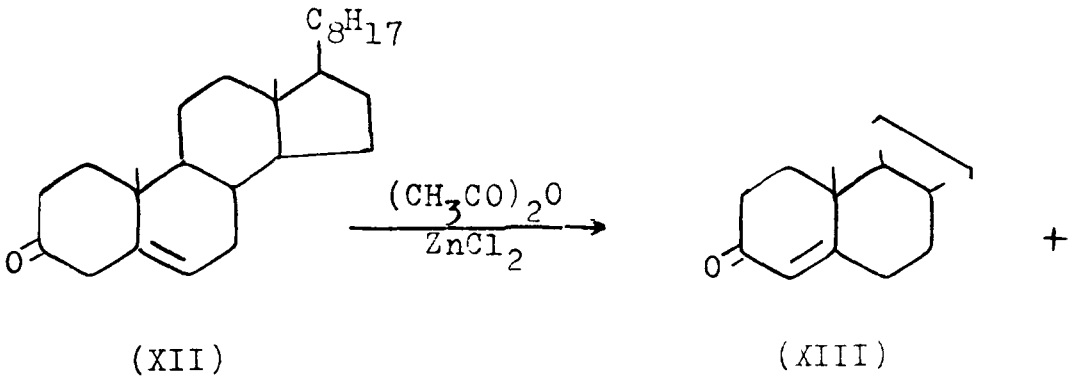
No reaction.

(X)

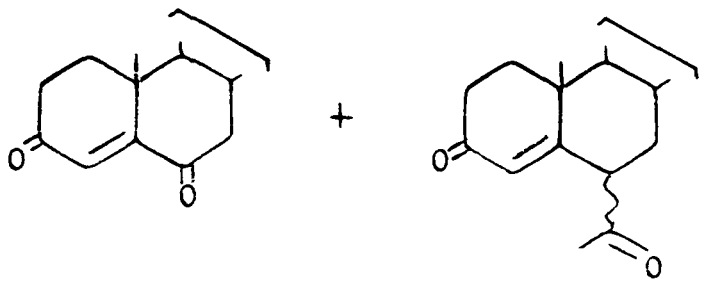


No reaction.

(X)



(XII) (XIII)



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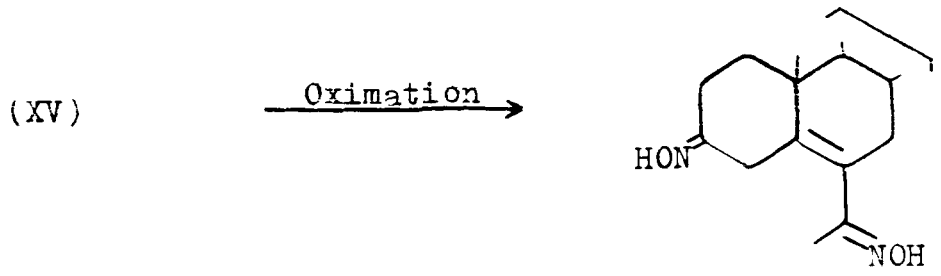

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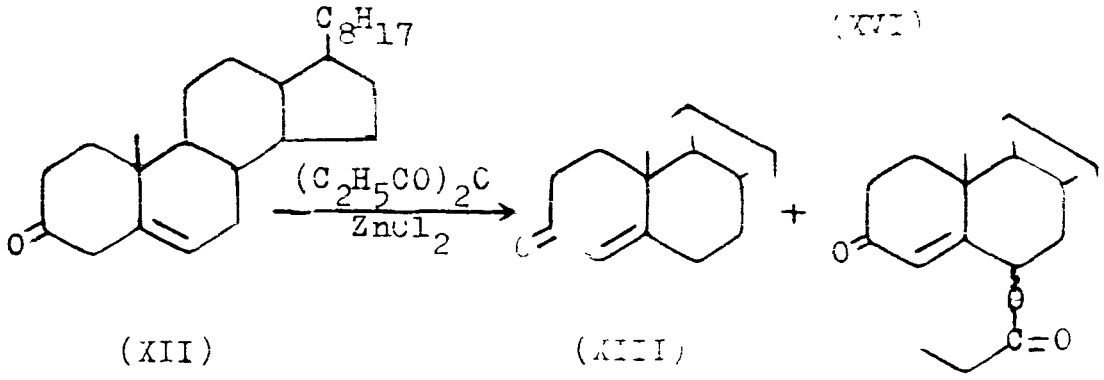


(XII) (XIII)

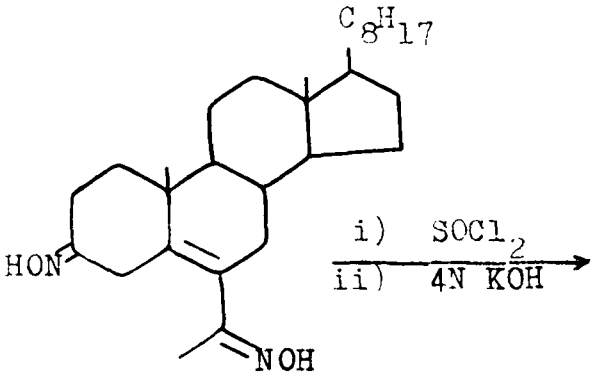
(XVII)

PART - I(B)

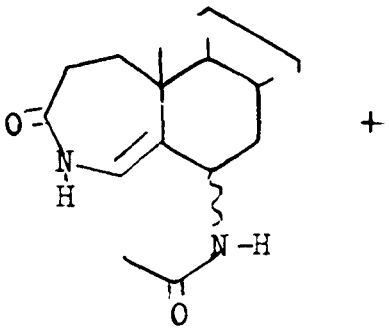
AZASTEROIDS

Previous work from our laboratory has described the Beckmann rearrangement and the Schmidt reaction of several steroidal ketoximes and ketones, respectively in order to prepare azasteroids with possible biological potential. The work was mainly concerned with the cholestane and stigmastane series and as a consequence a large number of the then unknown azastreoids were synthesized.

As an extension of the above work, steroidal ketones, suchas, 6ξ-acetylcholest-4-en-3-one (XV) and 2,6-dibromocholest-1,4,6-trien-3-one (XXI) and ketoxime, 6-acetylcholest-5-en-3-one-1',3-dioxime (XVI) were subjected to the Schmidt reaction and the Beckmann rearrangement, respectively, in order to prepare hitherto unsynthesized azasteroids. The characterization of the products thus obtained was done on the basis of their elemental analysis and spectral properties.



(XVI)



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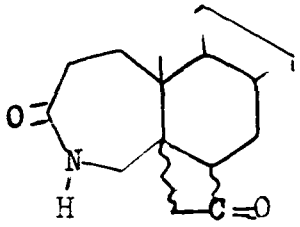
(XVIII)



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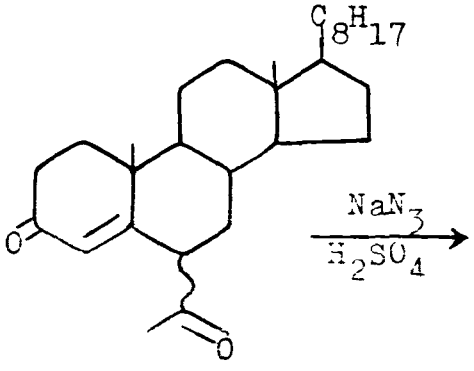

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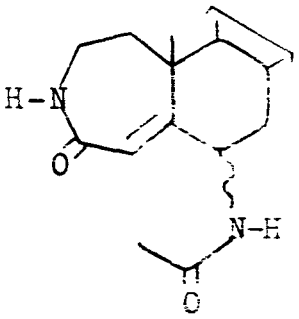
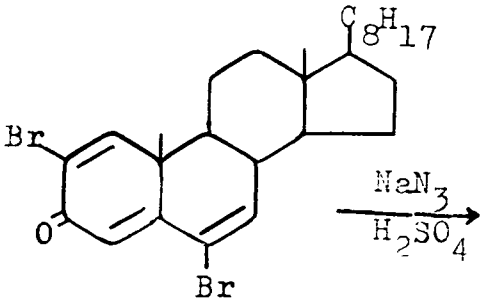
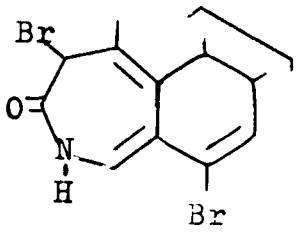


(XX)

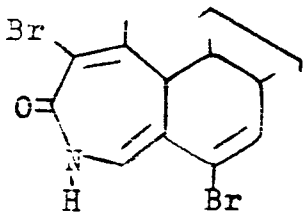


(XXI)



(XXII)

+



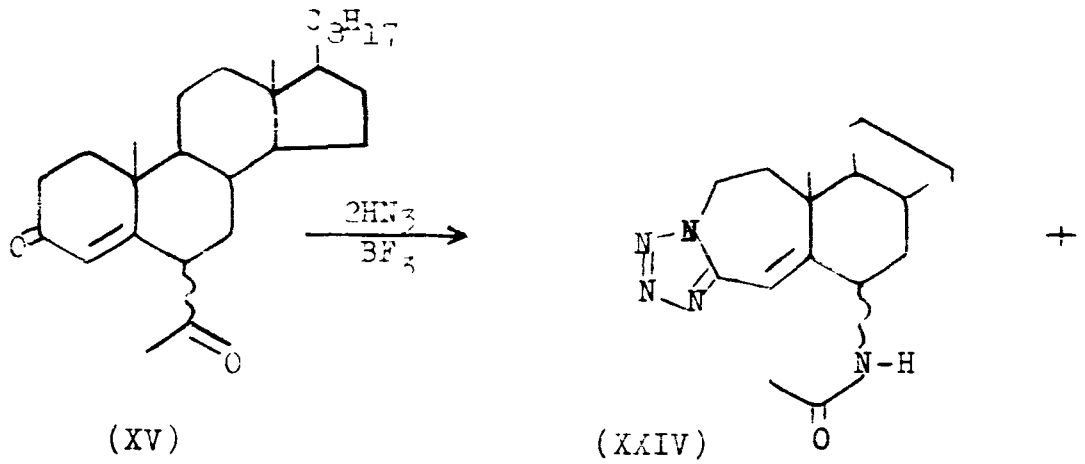
(XXIII)

PART - II

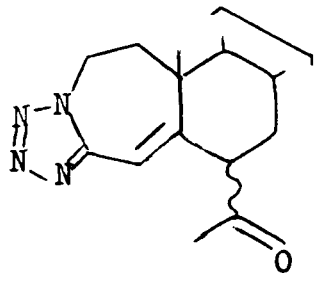
TETRAZOLOSTEROIDS

In recent years much attention has been paid towards the formation of steroidal tetrazoles because of the significant biological properties associated with a number of tetrazoles and their use as potential drugs. As a result of this several papers describing the synthesis of tetrazoles from various steroidal ketones have appeared from our laboratory also.

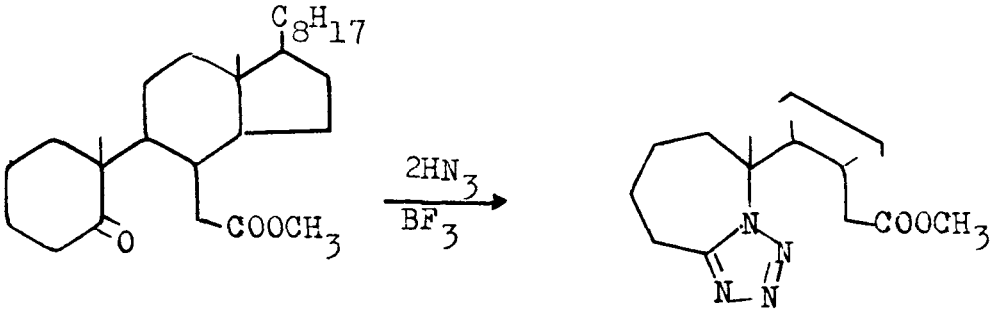
This chapter is an extension of the above work on the synthesis of tetrazoles from the cholestane series. It describes the reaction of the steroidal ketones, 6ξ-acetyl-cholest-4-en-3-one (XV) and seco-ketoesters like methyl 5-keto-5,6-secocholestan-6-oate (XXVI) and methyl 5-keto-5,6-secocholest 3-en-6-oate (XXVIII) with an excess of hydrazoic acid in the presence of boron trifluoride as the catalyst. The products obtained from the above reactions have been characterized on the basis of their elemental analysis and spectral properties.



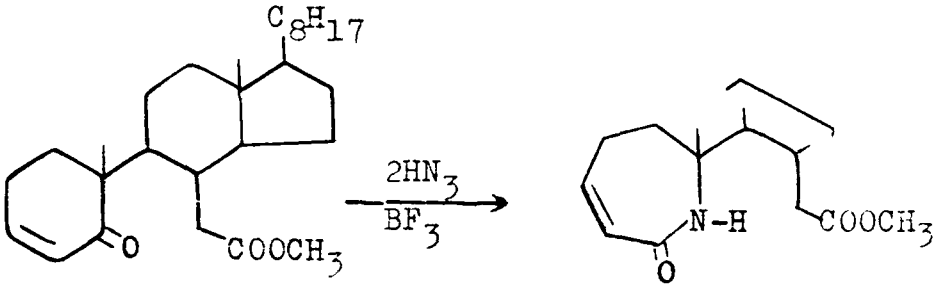
(XV) (XXIV)



(XXV)



(XXVI) (XXVII)



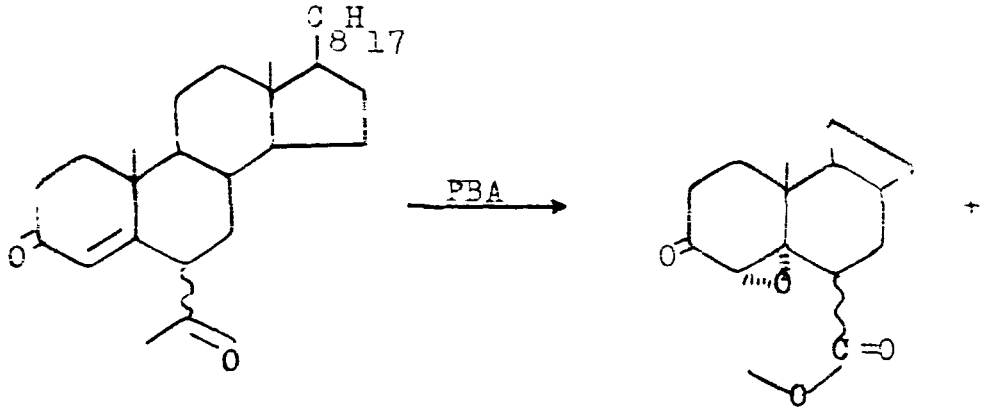
(XXVIII) (XXIX)

PART - III

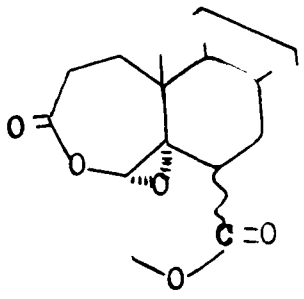
OXASTEROIDS

Previous work from our laboratory had described the Baeyer-Villiger oxidation of several ketones in order to prepare oxasteroids. The work was mainly concerned with the cholestane and the stigmastane series and as a result, a large number of the then unknown oxasteroids were synthesized.

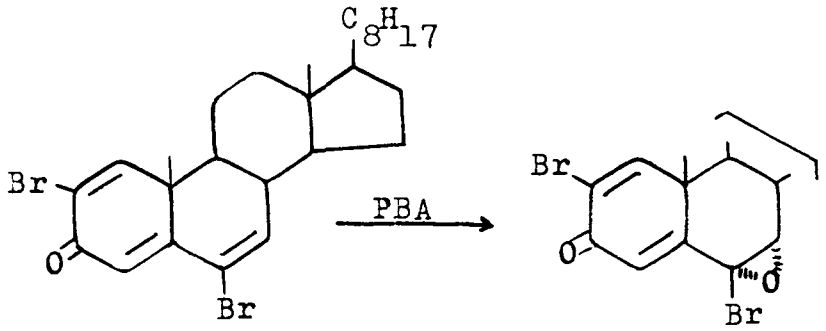
As an extension of the above work steroidal ketones, suchas 6ξ-acetylcholest-4-en-3-one (XV) and 2,6-dibromo-cholesta-1,4,6-trien-3-one (XXI) were subjected to the Baeyer-Villiger oxidation in order to get the corresponding oxasteroids. The characterization of the products thus obtained was done on the basis of their elemental analysis and spectral properties.



(XV) (XXX)



(XXXI)



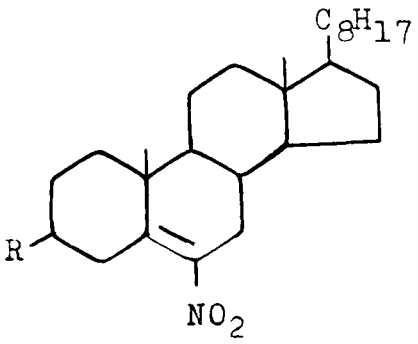
(XXI) (XXXII)

PART - IV

MASS SPECTRAL STUDIES ON STEROIDAL NITROOLEFINS

During the last twenty five years or so the mass spectrometry has developed to oecomea very powerful analytical tool in the characterization of organic compounds. Virtually, every class of organic compounds had been subjected to this study and useful structure-spectra relationships have been established. It was, however, found that no significant studies have been made on the mass spectrometry of steroidal nitro compounds and this prompted as to undertake such studies

on some of the structurally related steroidal nitro compounds. These included the steroidal nitroolefins suchas 6-nitrocholest-5-ene (XXXIII), 3β-chloro-6-nitrocholest-5-ene (XXXIV) and 3β-acetoxy-6-nitrocholest-5-ene (XXXV).



(XXXIII) R, H
(XXXIV) R, Cl
(XXXV) R, OAc

The proposed fragmentation pathways are supported in some cases by appropriate metastable peaks. The mechanisms suggested are only tentative in the absence of appropriate deuterated analogues and the accurate mass measurements.

THEORETICAL

PART - I

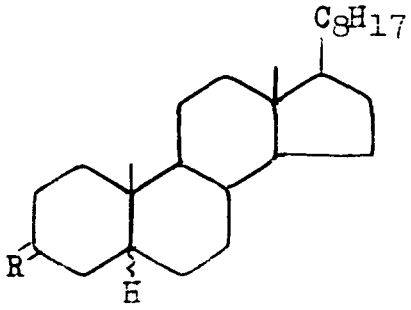
AZASTEROIDS

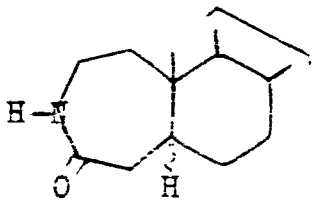
The steroidal compounds containing nitrogen as a part of the nucleus, commonly called azasteroids, have been synthesized by a variety of methods. The biological activities associated with such nitrogen containing steroids has drawn the attention of synthetic organic chemists and a very large number of azasteroids have been synthesized. Out of these many have shown potential biological activities and are of clinical significance. Some of these compounds have entered medical field as potent and reliable drugs. There are knwon azasteroids which have been found to exhibit antimicrobial, antihormonal, antihypercholesterolaenic, anticancer, neuromuscular blocking and anabolic activities.

Insertion of nitrogen atom into the steroidal framework has been affected mostly by the Beckmann rearrangement of steroidal ketoximes and Schmidt reaction of steroidal ketones. A compilation of the literature on various azasteroids prepared by the Beckmann rearragement and Schmidt reaction is given by Singh et al.[1] Photochemical reaction and microbiological amidations[2-6] have also been used for the preparation of different azasteroid analogues. Other ways like suitable reaction with the respective secoketo acids

and oxasteroids, imide synthesis, Curtius and Hofmann rearrangements, total synthesis etc. are also employed in the preparation of azasteroids. The biological activity of azasteroids has been reviewed by Alauddin and Martin Smith[7,8] and Sugrue[9]. It is not possible to go through all the literature on azasteroids in these pages and therefore only selective examples are being mentioned here.

The Schmidt reaction of 5α-cholestan-3-one (I) and its 5β-isomer (II) with sodium azide and polyphosphoric acid or the Beckmann rearrangement of their respective oximes (III) and (IV) in polyphosphoric acid provided the respective 3-azasteroids (V) and (VI)[10].





(I) R, O; 5α

(II) R, O; 5β

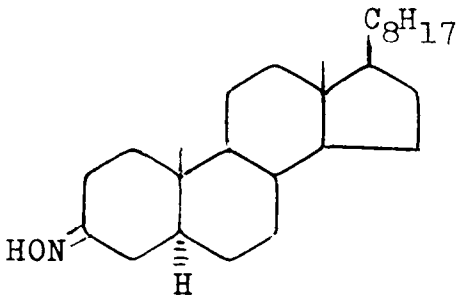
(III) R, NOH; 5α

(IV) R, NOH; 5β

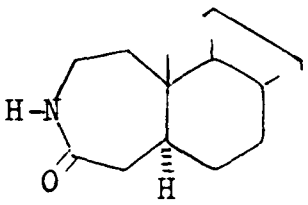
(V) 5α

(VI) 5β

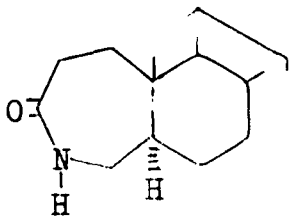
Later, Shoppee et al.[11] reported the formation of a mixture of the lactams, 3-aza-A-homo-5α-cholestan-4-one (V) and 4-aza-A-homo-5α-cholestan-3-one (VII) on Beckmann rearrangement of 5α-cholestan-3-one oxime (III).



(III)

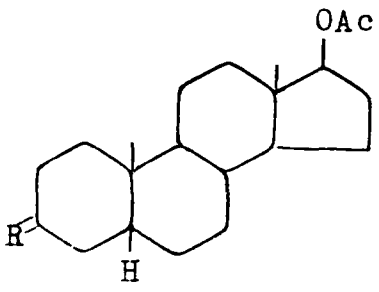


(V)



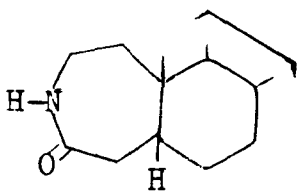
(VII)

Similarly, 17β-acetoxy-5β-androstan-3-one (VIII) on Schmidt reaction and its oxime (IX) on Beckmann rearrangement gave two isomeric lactams, (X) and (XI)[10,12-14].

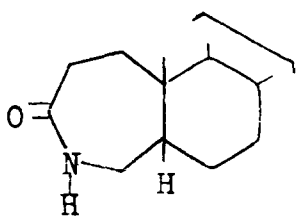


(VIII) R, O

(IX) R, NOH

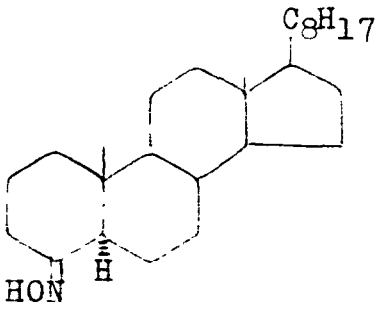


(X)

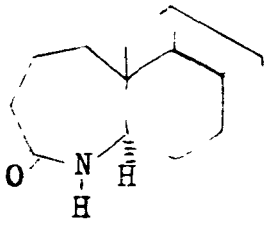


(XI)

When 5α-cholestan-4-one oxime (XII) was treated with thionyl chloride at -20°, the sole product of the reaction was 4a-aza-A-homo-5α-cholestan-4-one (XIII)[15].

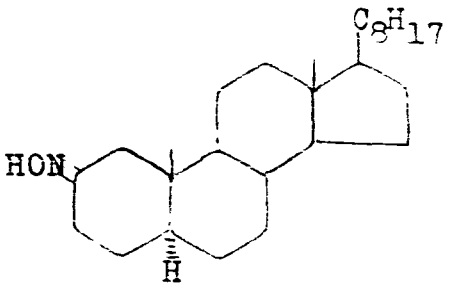


(XII)

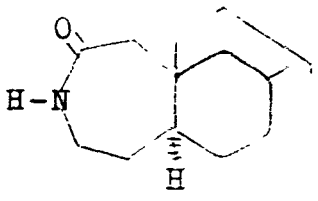


(XIII)

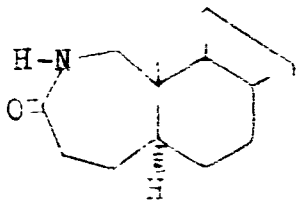
Two isomeric lactams, 3-aza-A-homo-5α-cholestan-2-one (XV) and 2-aza-A-homo-5α-cholestan-3-one (XVI) were obtained from the oxime of 5α-cholestan-2-one (XIV)[15].



(XIV)

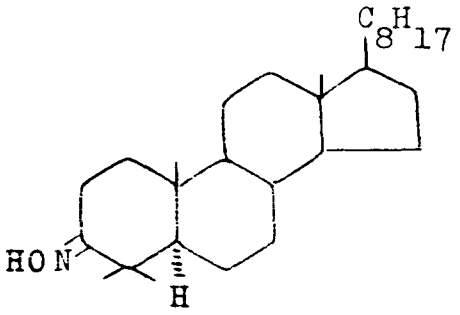


(XV)

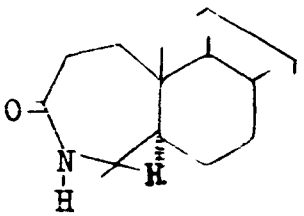


(XVI)

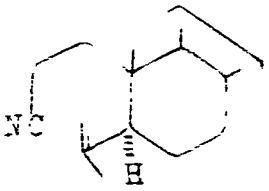
4,4-Dimethyl-5α-cholestan-3-one oxime (XVII) on the Beckmann rearrangement afforded, besides the normal product, 4-aza-A-homo-4a,4a-dimethyl-5α-cholestan-3-one (XVIII), a product of the second order Beckmann rearrangement, 3-cyano-4-methyl-A-nor-3,4-seco-5α-cholestan-4-ene (XIX)[16].



(XVII)

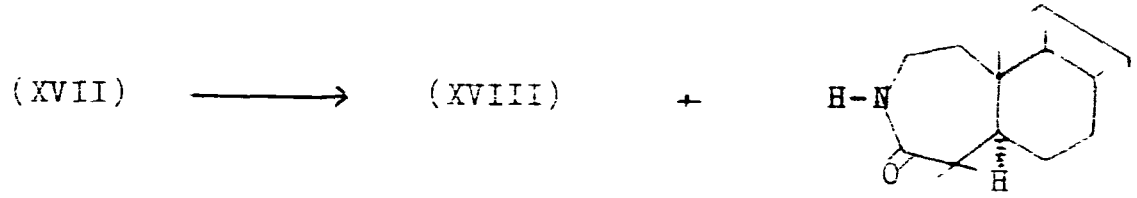


(XVIII)



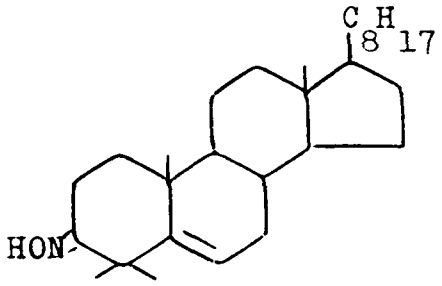
(XIX)

Photo-Beckmann rearrangement of (XVII)[17] gave two isomeric lactams (XVIII) and 3-aza-A-homo-4a,4a-dimethyl-5α-cholestan-4-one (XX).

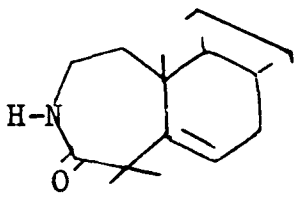


(XX)

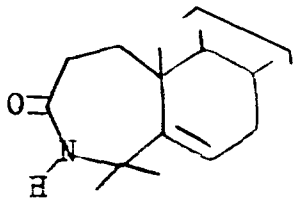
Photo-Beckmann rearrangement of 4,4-dimethylcholest-5-en-3-one oxime (XXI) provided two isomeric lactams, 3-aza-A-homo-4a,4a-dimethylcholest-5-en-4-one (XXII) and 4-aza-A-homo-4a,4a-dimethylcholest-5-en-3-one (XXIII)[18].



(XXI)

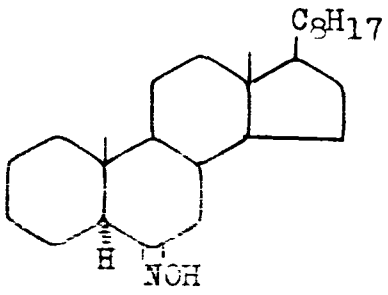


(XXII)

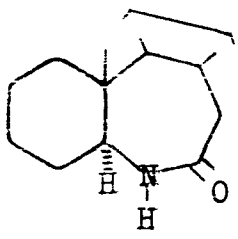


(XXIII)

5α-Cholestan-6-one oxime (XXIV) on Beckmann rearrangement afforded a single lactam, 6-aza-B-homo-5α-cholestan-7-one (XXV)[15].

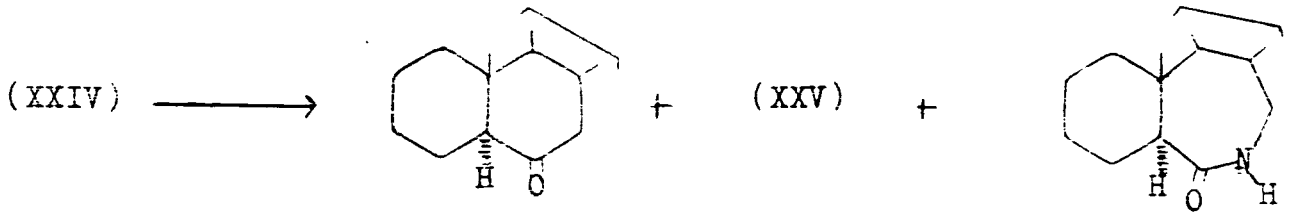


(XXIV)



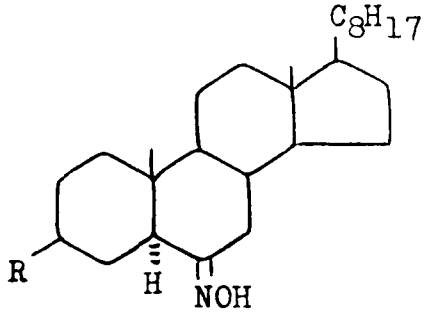
(XXV)

The photo-Beckmann rearrangement of ketoxime (XXIV)[19], however, afforded three products. Besides the starting oxime (XXIV) a trace of 5α-cholestan-6-one (XXVI) and two isomeric lactams, 6-aza-B-homo-5α-cholestan-7-one (XXV) and 7-aza-B-homo-5α-cholestan-6-one (XXVII) were obtained.

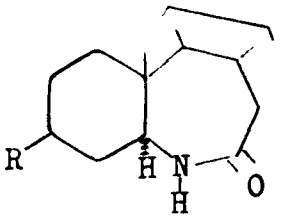


(XXVI) (XXVII)

Ahmad et al. carried out the Beckmann rearrangement of 3β-chloro-5α-cholestan-6-one oxime (XXVIII)[20], its 3β-bromo (XXIX)[21] and 3β-iodo (XXX)[22] analogues according to the methods of Craig and Naik[23] and obtained the corresponding lactams, 3β-chloro-6-aza-B-homo-5α-cholestan-7-one (XXXI), 3β-bromo-6-aza-B-homo-5α-cholestan-7-one (XXXII) and 3β-iodo-6-aza-B-homo-5α-cholestan-7-one (XXXIII), respectively.

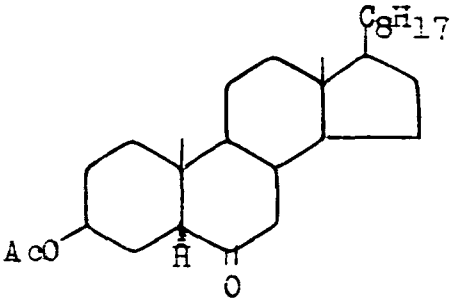


(XXVIII) R, Cl
(XXIX) R, Br
(XXX) R, I

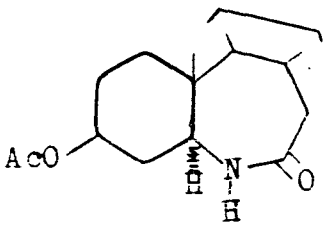


(XXXI) R, Cl
(XXXII) R, Br
(XXXIII) R, I

Doorenbos and Singh[24] carried out the Schmidt reaction of 3β-acetoxy-5α-cholestan-6-one (XXXIV) and obtained the lactam, 3β-acetoxy-6-aza-B-homo-5α-cholestan-7-one (XXXV) as the only product.

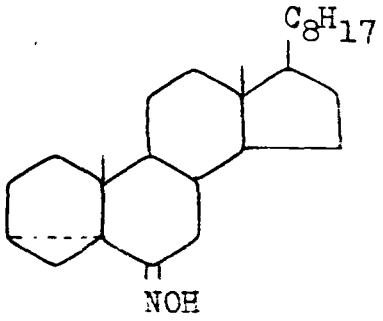


(XXXIV)

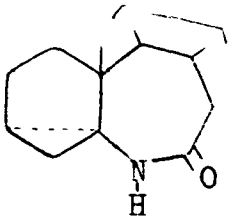


(XXXV)

The Beckmann rearrangement of 3α,5-cyclo-5α-cholestan-6-one oxime (XXXVI) provided the lactam, 6-aza-B-homo-3,5-cyclo-5α-cholestan-7-one (XXXVII)[21].



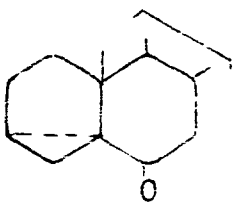
(XXXVI)



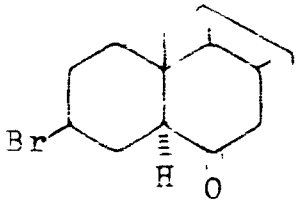
(XXXVII)

The lactam (XXXVII) undergoes "Retero-Beckmann rearrangement", the only example of its kind in literature[25]. When the lactam (XXXVII) was treated with HBr in boiling acetone, the oxime (XXXVI), a product of "Retero-Beckmann rearrangement', the cyclo ketone (XXXVIII) and the bromo ketone (XXXIX) were obtained.

(XXXVII) → (XXXVI) +

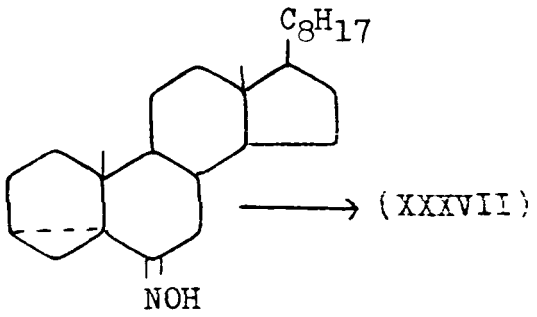


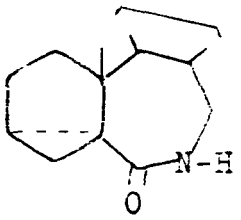
+



(XXXVIII) (XXXIX)

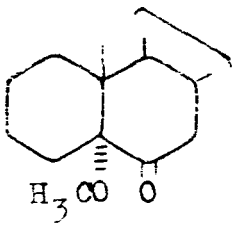
Suginome and coworkers[26] reported the photo-Beckmann rearrangement of the oxime (XXXVI). Besides the two expected lactams, (XXXVII) and (XL), they also obtained the cyclo ketone (XXXVIII), 5α-cholestan-6-one (XXVI), 5-methoxy-5α-cholestan-6-one (XLI) and cholest-4-en-6-one (XLII).

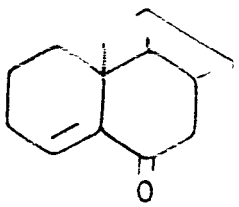


(XXXVI) → (XXXVII) + 

(XL) +

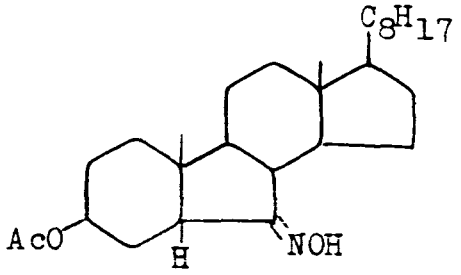
(XXXVIII) + (XXVI) +



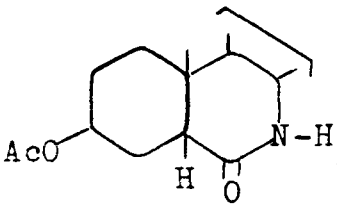
(XLI) + 

(XLII)

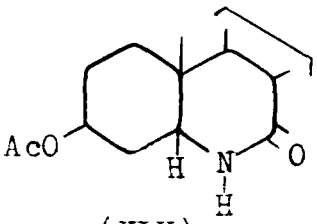
Morisawa[27] reported that 3β-acetoxy-B-nor-5β-cholestan-6-one oxime (XLIII) on the Beckmann rearrangement gave the two isomeric lactams, 3β-acetoxy-7-aza-5β-cholestan-6-one (XLIV) and 3β-acetoxy-6-aza-5β-cholestan-7-one (XLV).



(XLIII)

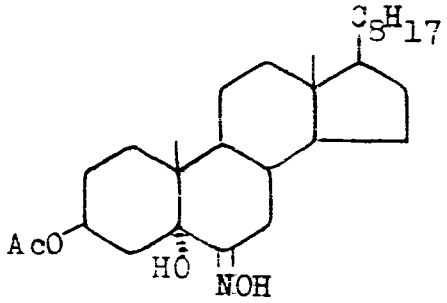


(XLIV)

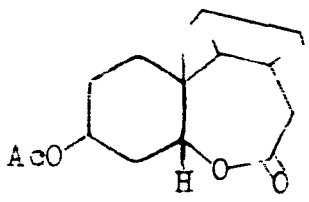


(XLV)

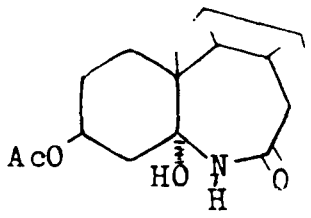
Photolysis of 3β-acetoxy-5-hydroxy-5α-cholestan-6-one oxime (XLVI) afforded 3β-acetoxy-6-oxa-B-homo-5β-cholestan-7-one (XLVII) (ε lactone), 3β-acetoxy-6-aza-B-homo-5-hydroxy-5α-cholestan-7-one (XLVIII) and 3β-acetoxy-7-aza-B-homo-5-hydroxy-5α-cholestan-6-one (XLIX)[28]. This shows a dramatic departure from a similar reaction observed with (XLVI). When subjected to the normal Beckmann rearrangement, (XLVI) gave the products of only second order Beckmann rearrangement[29].



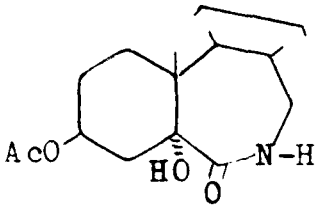
(XLVI)



(XLVII)

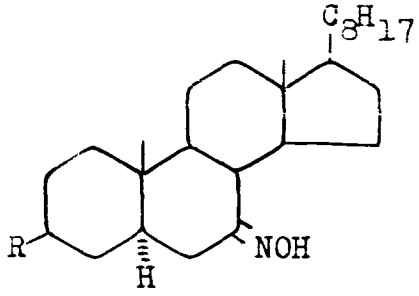


(XLVIII)



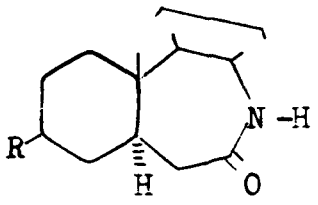
(XLIX)

5α-Cholestan-7-one oxime (L)[30] and its 3β-acetoxy (LI)[31] analogue on Beckmann rearrangement afforded the corresponding lactams, 7a,aza-B-homo-5α-cholestan-7-one (LII) and 3β-acetoxy -7a-aza-B-homo-5α-cholestan-7-one (LIII).



(L) R, H

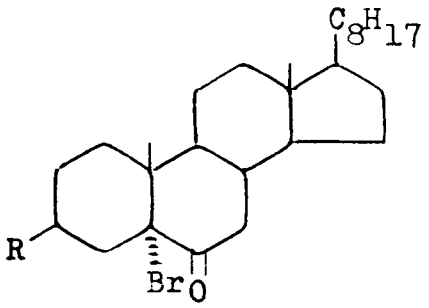
(LI) R, OAc



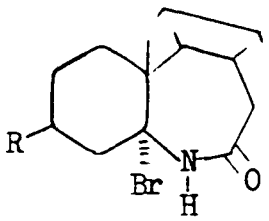
(LII) R, H

(LIII) R, OAc

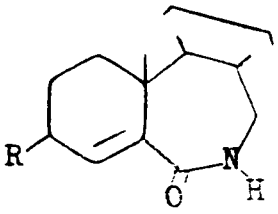
Schmidt reaction of 3β-acetoxy-5α-bromocholestan-6-one (LIV) afforded 3β-hydroxy-6-aza-B-homo-5α-bromocholestan-7-one (LV) and 5α-bromocholestan-6-one (LVI) gave the corresponding lactams, (LVII) and 7-aza-B-homocholest-4-en-6-one (LVIII)[32].



(LIV) R, OAc (LVI) R, H

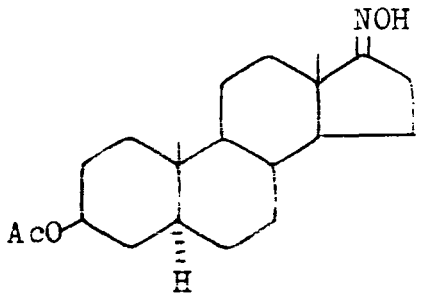


(LV) R, OH (LVII) R, H

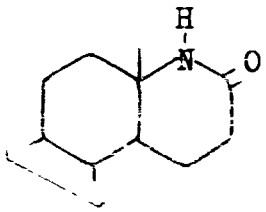


(LVIII) R, H

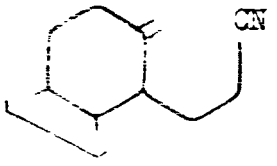
3β-Acetoxy-5α-androstan-17-one oxime (LIX) on the Beckmann rearrangement gave 3β-acetoxy-17a-aza-D-homo-5α-androstan-17-one (LX) and 17-cyano-3β-acetoxy-13,17-seco-5-androst-13(18)-ene (LXI)[16].



(LIX)

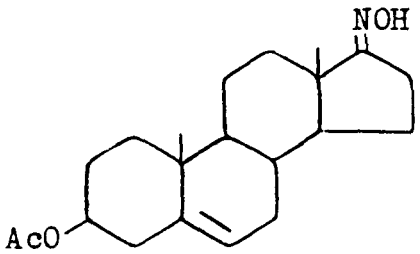


(LX)

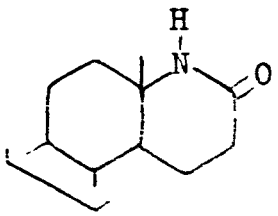


(LXI)

Anliker et al.[33] accomplished the Beckmann rearrangement of 3β-acetoxyandrost-5-en-17-one oxime (LXII) using p-acetaminobenzenesulphonyl chloride in pyridine and obtained 3β-acetoxy-17a-aza-D-homoandrost-5-en-17-one (LXIII). This lactam (LXIII) was also obtained from (LXII) on the Beckmann rearrangement using thionyl chloride in dioxan[34].

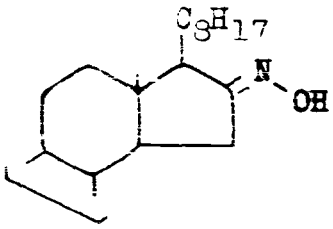


(LXII)

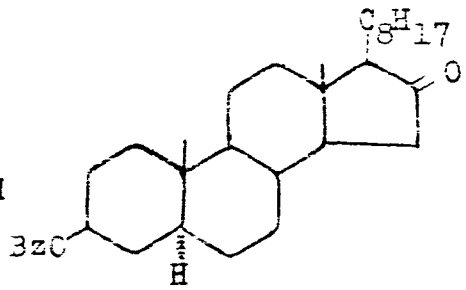


(LXIII)

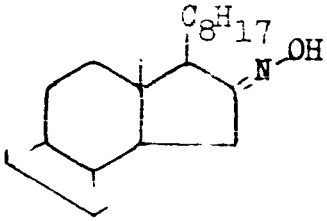
Tsuda and Hayatsu[35] prepared the syn- and anti-oximes from 3β-benzoxy-5α-cholestan-16-one (LXIV). The syn-oxime (LXV-a) provided 3β-benzoxy-16-aza-D-homo-5α-cholestan-17-one (LXVI) and the anti-oxime (LXV-b) afforded 3β-benzoxy-17-aza-D-homo-5α-cholestan-16-one (LXVII) on the Beckmann rearrangement.



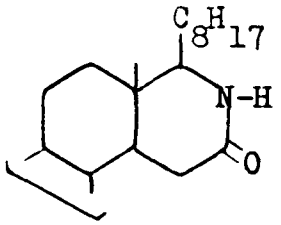
(LXV-b)



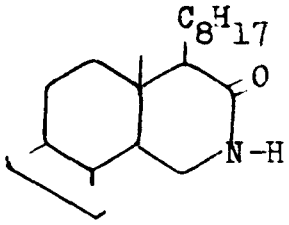
(LXIV)



(LXV-a)

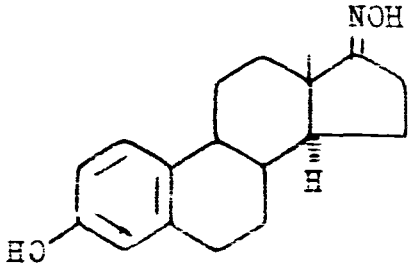


(LXVII)

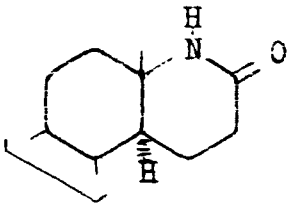


(LXVI)

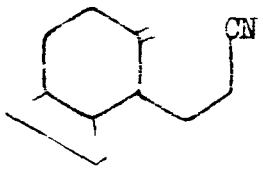
Bela and coworkers[36] obtained a lactam, 3-hydroxy-17a-aza-D-homoestra-1,3,5(10)-trien-17-one (LXIX) and the second order Beckmann product (LXX), when 3-hydroxyestra-1,3,5(10)-trien-17-one oxime (LXVIII) was heated with p-acetaminobenzenesulphonyl chloride in pyridine.



(LXVIII)

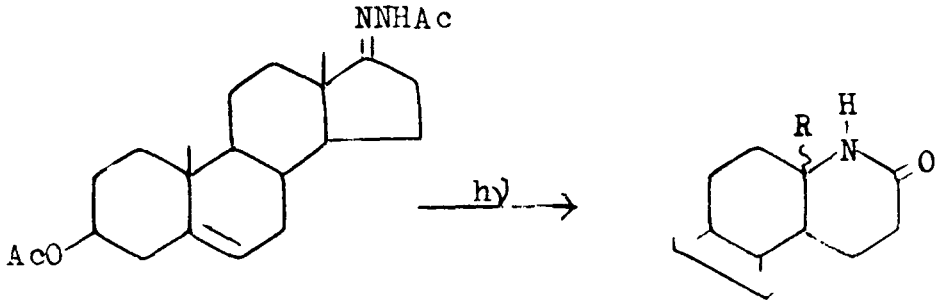


(LXIX)



(LXX)

The irradiation of the acetylhydrazone (LXXI) in dioxan in the presence of oxygen gave a mixture of the lactams (LXXII) and (LXXIII)[37].

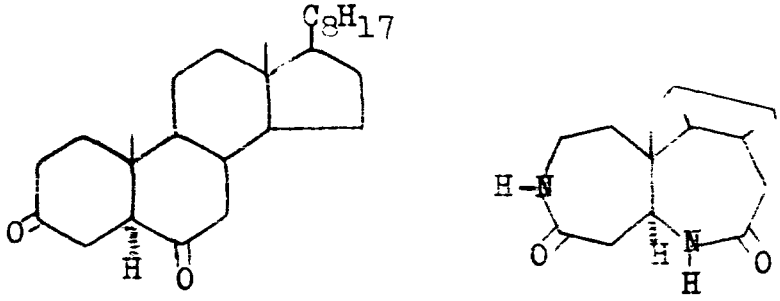


(LXXI)

(LXXII) R, α-CH_3

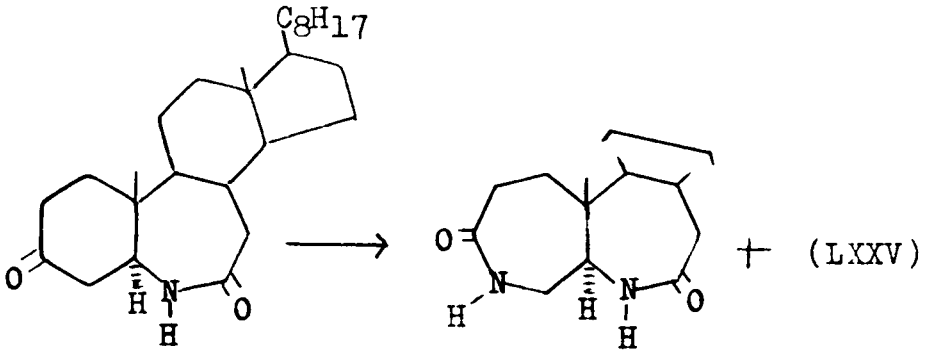
(LXXIII) R, β-CH_3

Doorenbos and Singh[24] prepared 3,6-diaza-A,B-bishomo-5α-cholestane-4,7-dione (LXXV) from 5α-cholestane-3,6-dione (LXXIV) by the Schmidt reaction using excess of hydrogen azide.



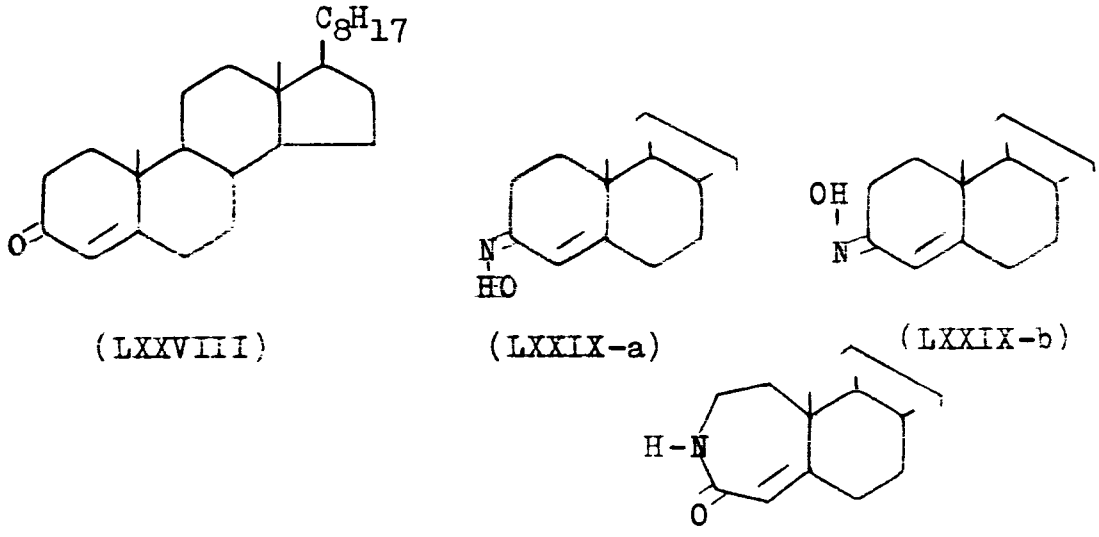
(LXXIV) (LXXV)

The Schmidt reaction of 6-aza-B-homo-5α-cholestane-3,7-dione (LXXVI) afforded two products, 4,6-diaza-A,B-bishomo-5α-cholestane-3,7-dione (LXXVII, and 3,6-diaza-A,B-bishomo-5α-cholestane-4,7-dione (LXXV)[38].



(LXXVI) (LXXVII) + (LXXV)

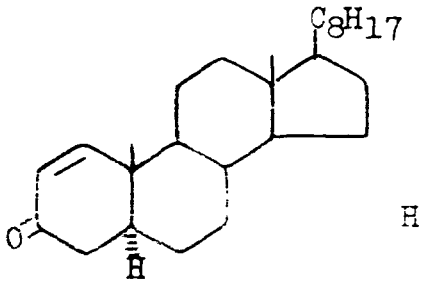
Shoppee et al.[11] observed that the Beckmann rearrangement of a mixture of α,β-unsaturated syn- (LXXIX-a) and anti- (LXXIX-b) oximes of cholest-4-en-3-one (LXXVIII) in the ratio 2:3 with thionyl chloride was facile, giving 3-aza-A-homo-cholest-4a-en-4-one (LXXX). However, the rearrangement of anti-oxime (LXXIX-b)[39] with p-acetaminobenzenesulphonyl chloride in pyridine was not realized.



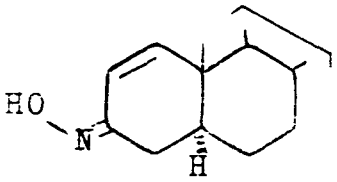
(LXXVIII) (LXXIX-a) (LXXIX-b)

(LXXX)

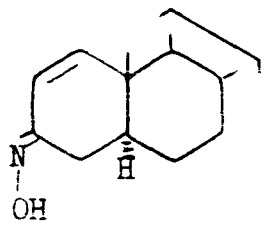
Shoppee et al.[40] observed that the pure anti-oxime (LXXXII-b) derived from 5α-cholestan-1-en-3-one (LXXXI) did not undergo the Beckmann rearrangement with thionyl chloride. However, a mixture of the syn- (LXXXII-a) and anti- (LXXXII-b) oximes on rearrangement gave single product, 4-aza-A-homo-5α-cholest-1-en-3-one (LXXXIII).



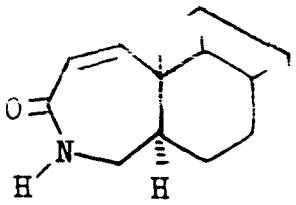
(LXXXI)



(LXXXII-a)



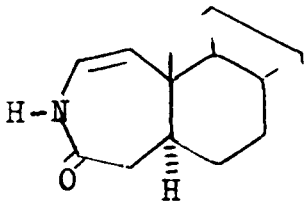
(LXXXII-b)



(LXXXIII)

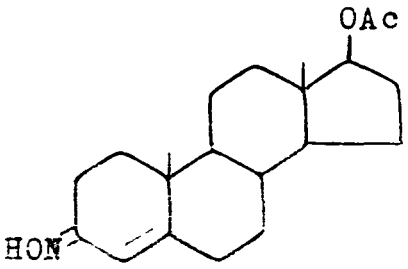
Kobayashi et al.[16] reinvestigated this reaction and found that the syn-oxime (LXXXII-a) with polyphosphoric acid gave (LXXXIII) while the anti-oxime (LXXXII-b) under similar conditions provided both 3-aza-A-homo-5α-cholest-1-en-4-one (LXXXIV) and (LXXXIII).

(LXXXII-a) ⟶ (LXXXIII)

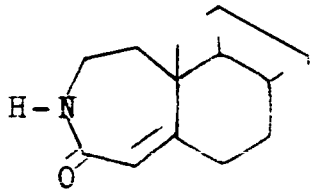
(LXXXII-b) ⟶  + (LXXXIII)

(LXXXIV)

Testosterone acetate oxime (LXXXV) on the Beckmann rearrangement with thionyl chloride furnished a single lactam, 17β-acetoxy-3-aza-A-homoandrost-4a-en-4-one (LXXXVI)[41].

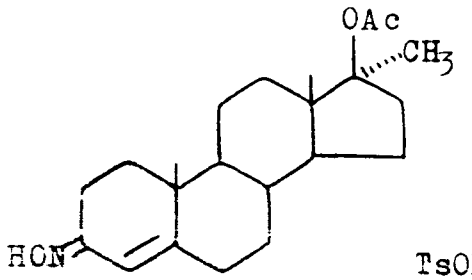


(LXXXV)

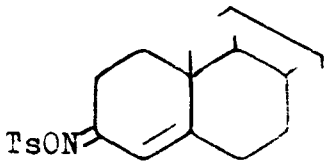


(LXXXVI)

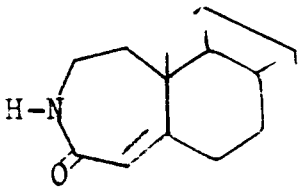
Kohen[42] performed the Beckmann rearrangement of 17β-acetoxy-17α-methylandrost-4-en-3-one oxime (LXXXVII) with p-toluenesulphonyl chloride in dimethylformamide and obtained the corresponding oxime tosylate (LXXXVIII) and 17β-acetoxy-17α-methyl-3-aza-A-homoandrost-4a-en-4-one (LXXXIX).



(LXXXVII)

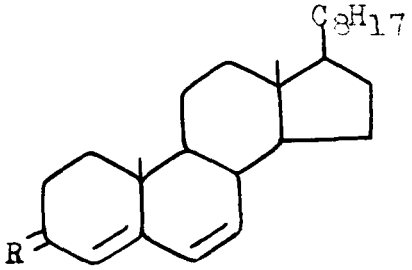


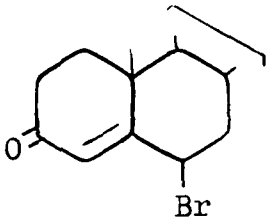
(LXXXVIII)

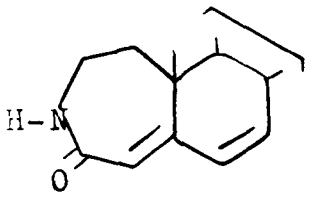


(LXXXIX)

Ahmad et al.[43] reported the Schmidt reaction of cholesta-4,6-dien-3-one (XC), and the Beckmann rearrangement of the corresponding oxime (XCI). They obtained the same lactam, 3-aza-A-homocholesta-4a,6-dien-4-one (XCIII) in both the cases. The same lactam (XCIII) was also obtained from the Schmidt reaction of 6β-bromocholest-4-en-3-one (XCII). The ketone (XCII) also provided the oxime (XCI); obviously dehydrobromination occurred under the reaction conditions.

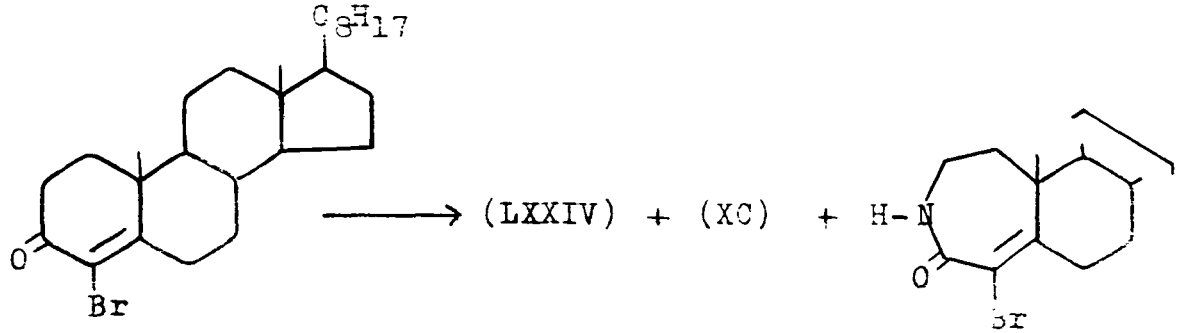






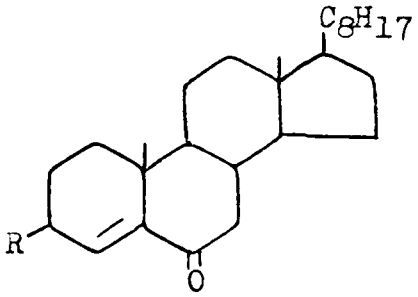
(XC) R, O (XCII) (XCIII)
(XCI) R, NOH

4-Bromocholest-4-en-3-one (XCIV) with sodium azide and polyphosphoric acid afforded 5α-cholestane-3,6-dione (LXXIV), cholesta-4,6-dien-3-one (XC) and the lactam, 3-aza-4a-bromo-A-homocholest-4a-en-4-one (XCV), a product of the normal Schmidt reaction[44].



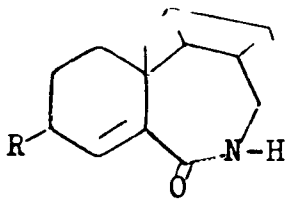
(XCIV) (XCV)

Ahmad et al.[20,22] carried out the Schmidt reaction of cholest-4-en-6-one (XLII) and its 3β-acetoxy (XCVI) analogue and obtained the corresponding lactams, 7-aza-B-homocholest-4-en-6-one (LVIII) and 3β-acetoxy-7-aza-B-homocholest-4-en-6-one (XCVII).



(XLII) R, H

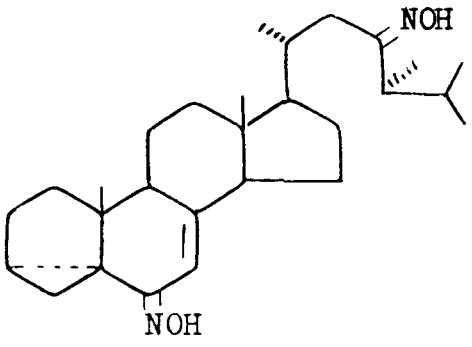
(XCVI) R, OAc



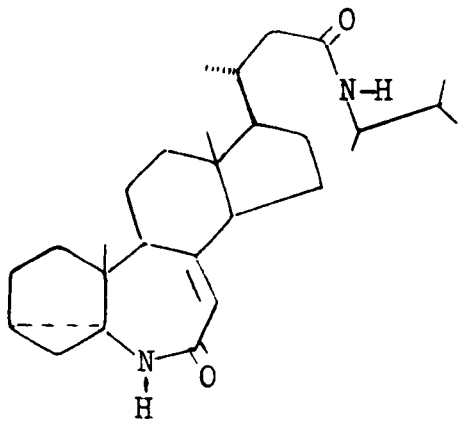
(LVIII) R, H

(XCVII) R, OAc

Barton et al.[45] observed that 3α,5-cyclo-5α-ergost-7-ene-6,23-dione dioxime (XCVIII) gave the diaza compound, 6,23a-diaza-3α,5-cyclo-B-homo-5α-ergost-7a-ene-7,23-dione (XCIX) as the only product when an excess p-toluenesulphonyl chloride was used for the rearrangement.

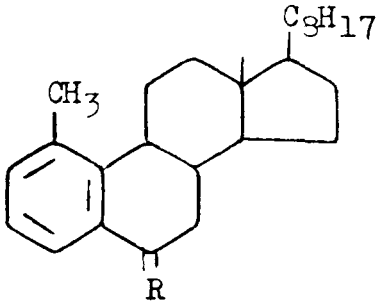


(XCVIII)



(XCIX)

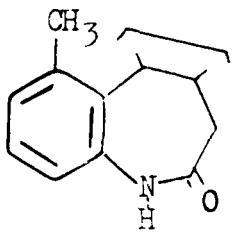
The Schmidt reaction of 1-methyl-19-norcholesta-1,3, 5(10)-trien-6-one (C) or the Beckmann rearrangement of the corresponding oxime (CI) and oxime tosylate (CII) provided 6-aza-B-homo-1-methyl-19-norcholesta-1,3,5(10)-trien-7-one (CIII)[46].



(C) R, O

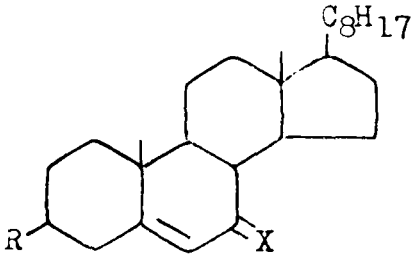
(CI) R, NOH

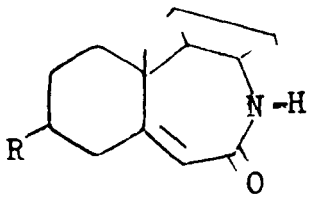
(CII) R, NOTs



(CIII)

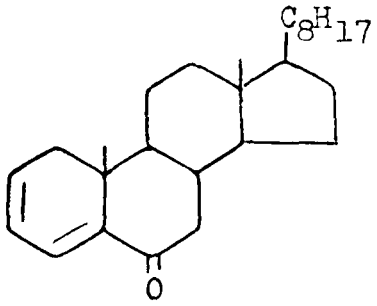
3β-Acetoxycholest-5-en-7-one (CIV) gave a single oxime (CVI) which on Beckmann rearrangement with p-toluenesulphonyl chloride and pyridine gave 3β-acetoxy-7a-aza-B-homocholest-5-en-7-one (CVIII)[47,48]. Similar results were obtained when the oximes (CVI)[49] and (CVII)[30] were treated with thionyl chloride. Matkovics et al.[31] reported the formation of 3β-hydroxy-7a-aza-B-homocholest-5-en-7-one (CX) along with (CVIII) from the oxime (CVI). The lactam (CVIII) was also obtained by the Schmidt reaction of the ketone (CIV).



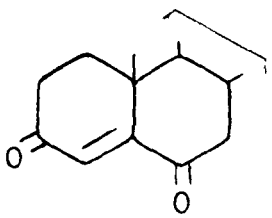


(CIV)	R, OAc;	X, O	(CVIII)	R, OAc
(CV)	R, H ;	X, O	(CIX)	R, H
(CVI)	R, OAc;	X, NOH	(CX)	R, OH
(CVII)	R, H ;	X, NOH		

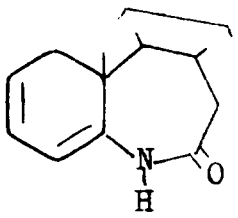
Cholesta-2,4-dien-6-one (CXI) on treatment with sodium azide (1 mole) and polyphosphoric acid afforded three products, cholest-4-ene-3,6-dione (CXII), 6-aza-B-homocholesta-2,4-dien-7-one (CXIII), the product of the normal Schmidt reaction and 6-aza-B-homocholest-4-ene-3,7-dione (CXIV)[50].



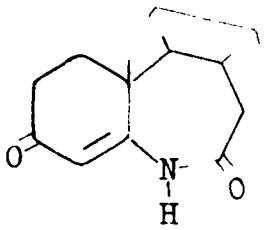
(CXI)



(CXII)

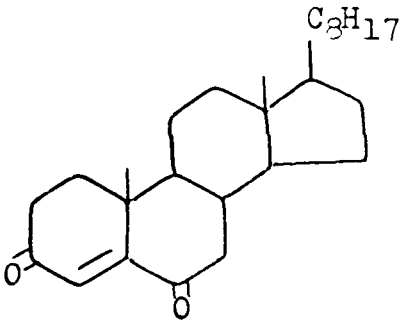


(CXIII)

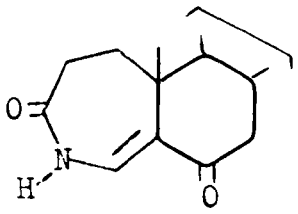


(CXIV)

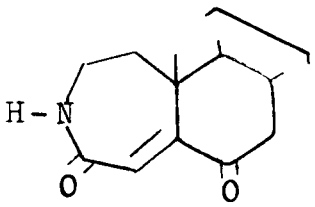
The Schmidt reaction of the ketone (CXII) provided 4-aza-A-homocholest-4a-ene-3,6-dione (CXV), 3-aza-A-homocholest-4a-ene-4,6-dione (CXVI) and the dilactam, 4,6-diaza-A,B-bishomocholest-4a-ene-3,7-dione (CXVII)[50,51].



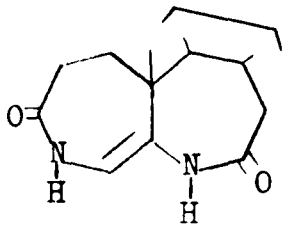
(CXII)



(CXV)

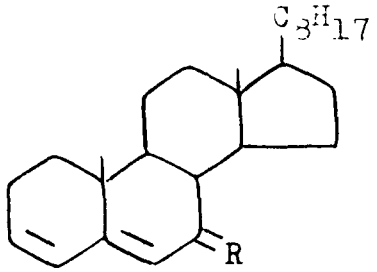


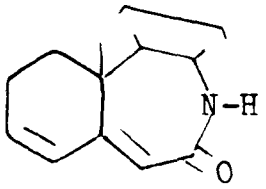
(CXVI)



(CXVII)

Cholesta-3,5-dien-7-one (CXVIII) gave a single oxime (CXIX) which on Beckmann rearrangement afforded 7a-aza-B-homocholesta-3,5-dien-7-one (CXX)[52].



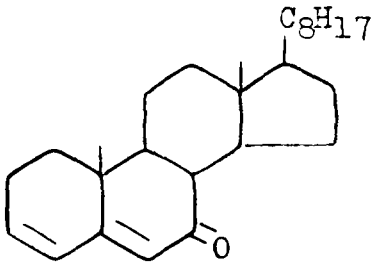


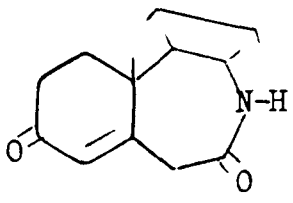
(CXVIII) R, O

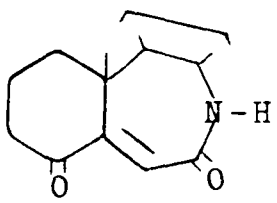
(CXIX) R, NOH

(CXX)

Schmidt reaction of the ketone (CXVIII) with sodium azide (3 mole equivalent) and polyphosphoric acid provided two lactams, 7a-aza-B-homocholest-4-ene-3,7-dione (CXXI) and 7a-aza-B-homocholest-5-ene-4,7-dione (CXXII)[53].

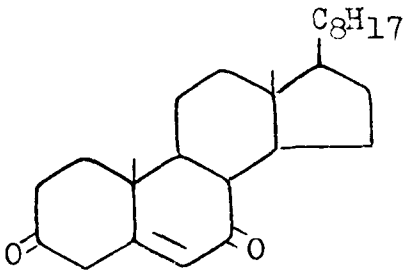




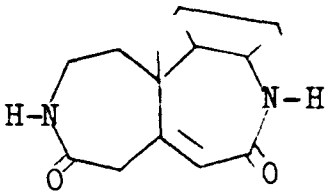


(CXVIII) (CXXI) (CXXII)

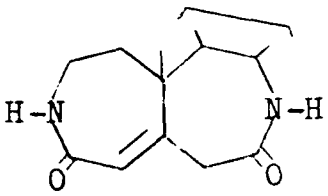
The treatment of cholest-5-ene-3,7-dione (CXXIII) with sodium azide in polyphosphoric acid provided a single product which could be either 3,7a-diaza-A,B-bishomocholest-5-ene-4,7-dione (CXXIV) or 3,7a-diaza-A,B-bishomocholest-4a-ene-4,7-dione (CXXV)[54].



(CXXIII)

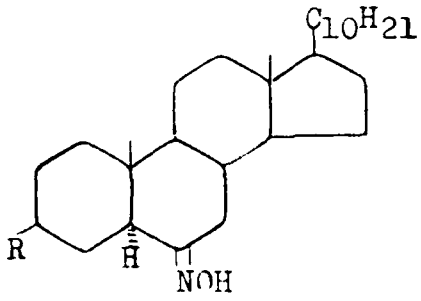


(CXXIV)



(CXXV)

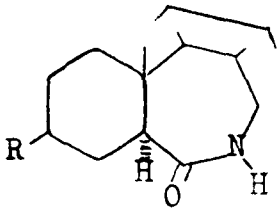
Recently, the stigmastane series has also been investigated[55,56]. The ketoximes subjected to the Beckmann rearrangement in this series are, 3β-acetoxystigmastan-6-one oxime (CXXVI) its 3β-chloro (CXXVII) and 3β-hydroxy (CXXVIII) analogues, 3α,5-cyclo-5α-stigmastan-6-one oxime (CXXIX), 3β-acetoxystigmast-4-en-6-one oxime (CXXX), 3β-acetoxystigmast-5-en-7-one oxime (CXXXI) and its 3β-chloro (CXXXII) analogue. All these oximes provided the corresponding Beckmann products (CXXXIII-CXL).



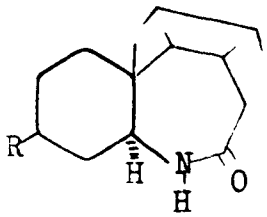
(CXXVI) R, OAc

(CXXVII) R, Cl

(CXXVIII) R, OH

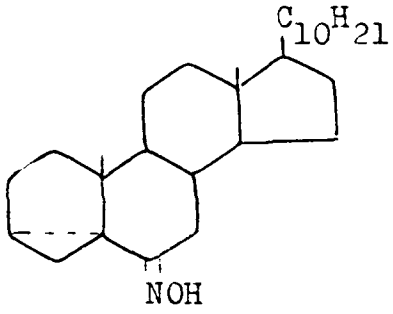


(CXXXIII) R, OAc

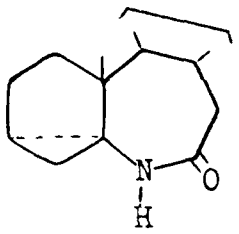


(CXXXIV) R, Cl

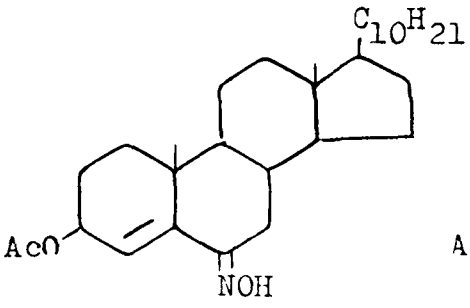
(CXXXV) R, OH



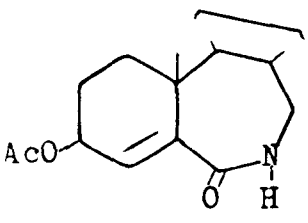
(CXXIX)



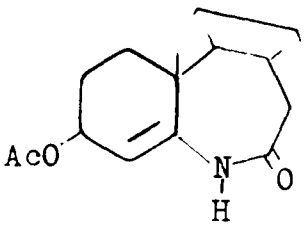
(CXXXVI)



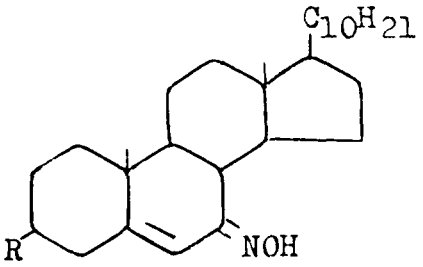
(CXXX)

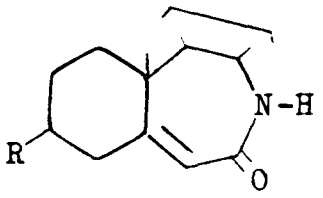


(CXXXVII)



(CXXXVIII)





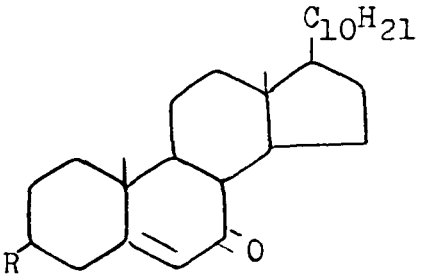
(CXXXI) R, OAc

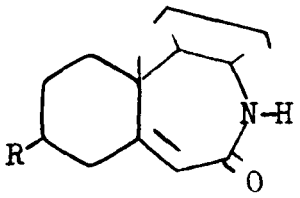
(CXXXII) R, Cl

(CXXXIX) R, OAc

(CXL) R, Cl

The Schmidt reaction of stigmast-5-en-7-one (CXLI) and its 3β-chloro (CXLII) analogue also provided the expected lactams, (CXLIII) and (CXL) respectively[56].





(CXLI) R, H

(CXLII) R, Cl

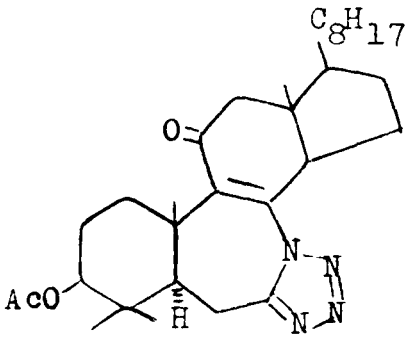
(CXLIII) R, H

(CXL) R, Cl

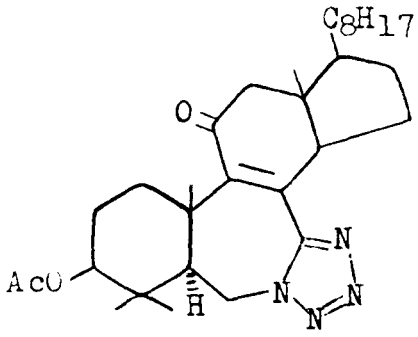
PART - II

TETRAZOLO STEROIDS

Steroidal compounds consisting of a five membered doubly unsaturated heterocycle with one carbon and four nitrogen atoms are termed as "Tetrazolo steroids". Probably the first example of the formation of a tetrazole in steroid and terpenoid field was given by Barnes et al.[57], in 1952. They reported the formation of a tetrazole (CXLIV) or (CXLV) the structure, however, was not established.



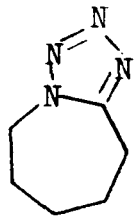
(CXLIV)



(CXLV)

Benson[58] has given an excellent review touching upon almost every aspect of tetrazole chemistry.

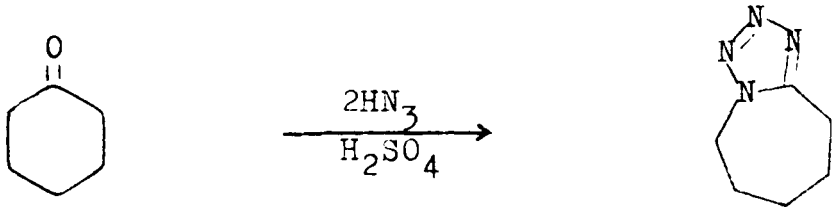
Tetrazoles enjoy important biological as well as non biological applications. These have been applied in various explosives and in propellants. Various tetrazole salts have been claimed for use in primers. They are of use in fibre, dyestuff and textile industries and have applications in photography also. On the biological side, the best known is pentamethylene tetrazole (Metrazole) (CXLVII) which is a potent stimulant of the central nervous system and is used clinically to counteract intoxication due to over dosage of barbiturates[59]. Stimulant, depressant, sedative and analgesic activities are shown by certain tetrazoles. Anti convulsant, hypotensive and andrenergic blocking action is exhibited by a number of 5-mono substituted tetrazoles[58].



(CXLVII)

Organic chemists, realising the above mentioned applications, directed their efforts towards the synthesis of terazoles. One of the most valuable methods discovered by Schmidt[60] for the preparation of tetrazoles is the rearrangement reaction between ketones and hydrazoic acid in the presence of strong acids. When one mole of hydrogen azide reacts with

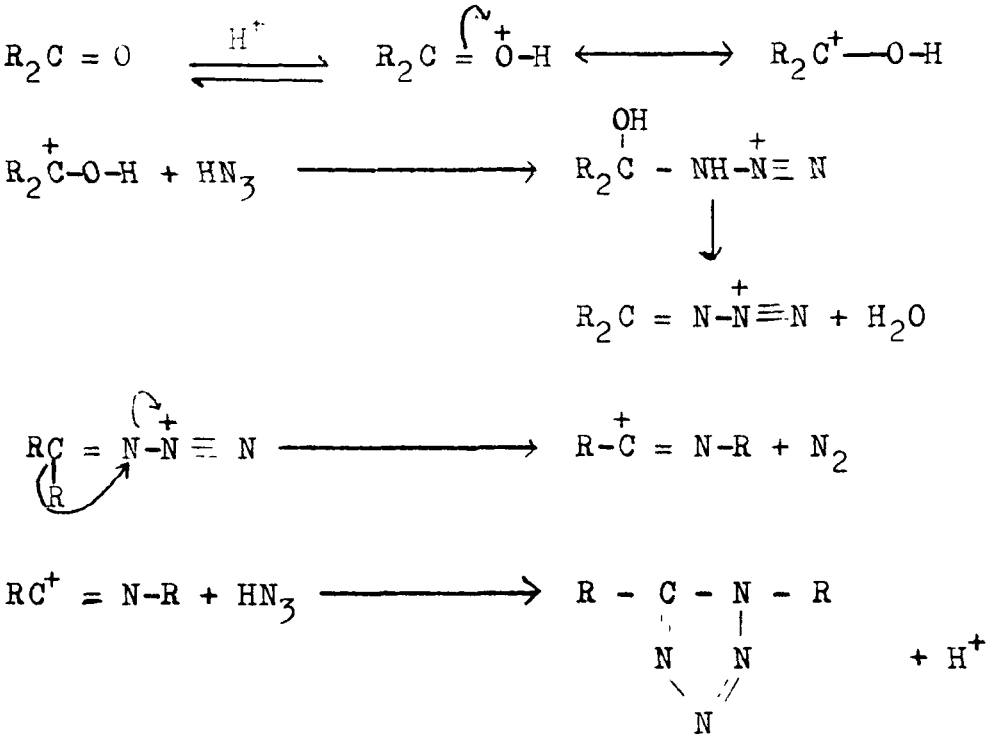
one mole of a carbonyl compound, N-substituted amides are formed; with two or more moles of hydrogen azide, tetrazoles are formed. The reaction has found its most extensive application with cyclic ketones with which yields are generally better than with acyclic ketones. Pentamethylene tetrazole (CXLVII) may be obtained from cyclohexanone (CXLVI) by this procedure[61].



(CXLVI) (CXLVII)

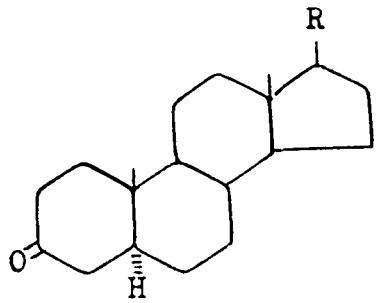
Smith[62] has advanced a probable mechanism for this transformation. The first step is the conversion of the carbonyl compound to a carbonium ion under the influence of the acid catalyst. This is followed by combination with one molecule of hydrazoic acid (functioning as a base), dehydration of the intermediate and rearrangement to an imidocarbonium ion, with simultaneous loss of nitrogen. When tetrazole formation occurs, a second molecule of hydrazoic acid reacts with the imidocarbonium ion, the positive charge is neutralized by the loss of a proton. The imidocarbonium ion intermediate

affords tetrazole and lactam by competing reaction with hydrazoic acid and water, respectively. The mechanism accounts satisfactorily for the necessity of using strong acid as catalyst.



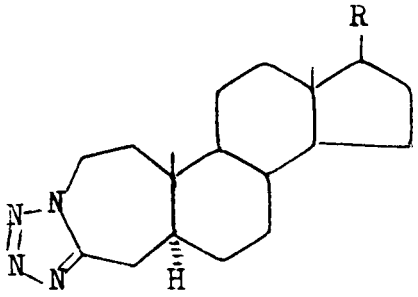
Steroidal tetrazoles did not attract the attention of synthetic organic chemists untill 1968 when Mechoulam[63] reported the synthesis of a number of ring A fused steroidal tetrazoles and claimed that some of them possessed anti-fertility and antispermatogenic activity. Mechoulam subjected 5α-cholestan-3-one (I) and 17β-hydroxy-5α-androstan-3-one (CXVIII) to Schmidt reaction using an excess of hydrazoic acid and obtained mixtures of isomeric tetrazoles (CXLIX, CL) and (CLI, CLII), respectively, containing 3-aza-A-homo[3,4-d]

tetrazole and 4-aza-A-homo[4,3-d]tetrazole system.



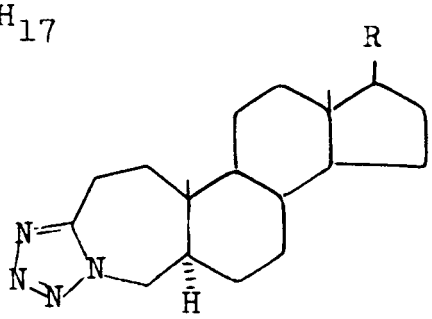
(I) R, C_8H_{17}

(CXLVIII) R, OH



(CXLIX) R, C_8H_{17}

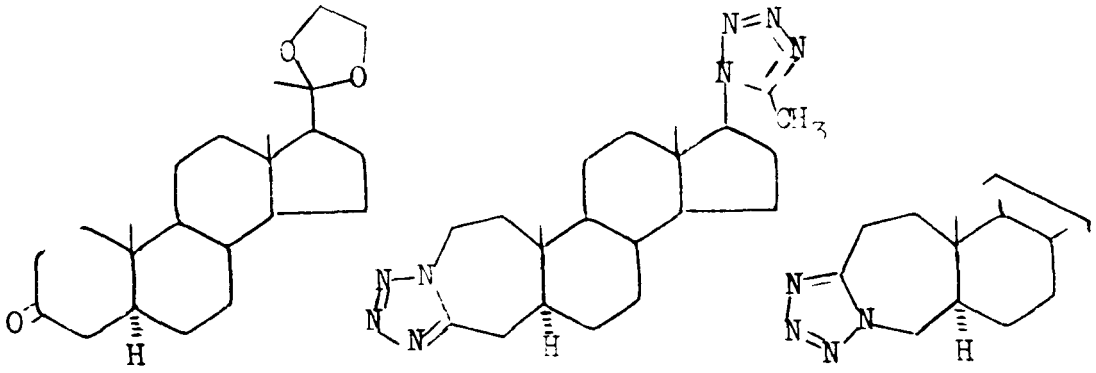
(CL) R, OH



(CLI) R, C_8H_{17}

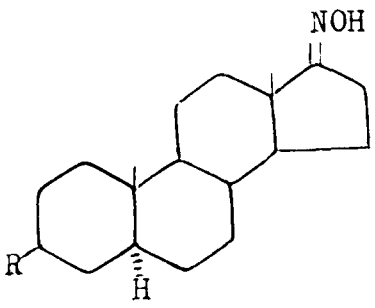
(CLII) R, OH

20,20-Ethylenedioxy-5α-pregnan-3-one (CLIII), under similar conditions afforded a mixture of 17β-(5-methyl tetrazole-1-yl)-3-aza-A-homo-5α-androstano[3,4-d]tetrazole (CLIV) and its 4-aza-isomer (CLV). The acetal ring at C_{20} is hydrolysed under acidic condition to C_{20} ketone which reacts further with hydrazoic acid to form tetrazole at 17-position[63].

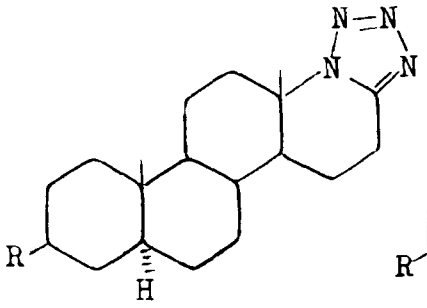


(CLIII) (CLIV) (CLV)

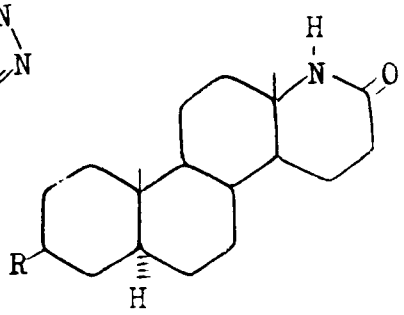
The realisation of the pharmacological potential of steroidal tetrazole prompted the organic chemists towards their synthesis and subsequently several papers appeared concerning their synthesis and biological activity. Crabbe et al.[64] of Syntex Group reported the formation of ring D fused tetrazoles from the reaction of 17-ketoximes with an excess of sodium azide in the presence of sulphuric acid. The reaction of 5α-androstan-17-one oxime (CLVI) was shown to afford the tetrazole, 17a-aza-D-homo-5α-androstano [17a,17-d]tetrazole (CLVII) and the D-homolactam (CLVIII). Similarly, the oxime (LIX) yielded 3β-acetoxy-17a-aza-D-homo-5α-androstano[17a,17-d]tetrazole (CLIX) and the lactam (LX) while the oxime (CLX) was shown to furnish the tetrazole 17a-aza-3-hydroxy-D-homoestra-1,3,5(10)-trieno[17a,17-d] tetrazole-3-methyl ether (CLXI) along with the seco-nitrile (CLXII) and the lactam (CLXIII).



(CLVI) R , H



(CLVII) R, H

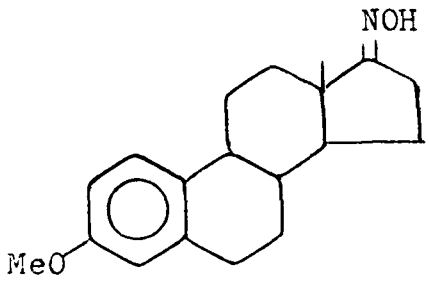


(CLVIII) R, H

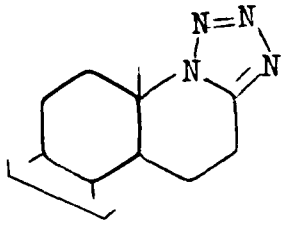
(LIX) R, OAc

(CLIX) R, OAc

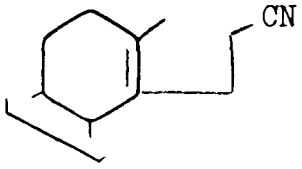
(LX) R, OAc



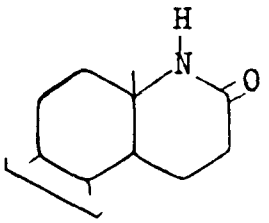
(CLX)



(CLXI)



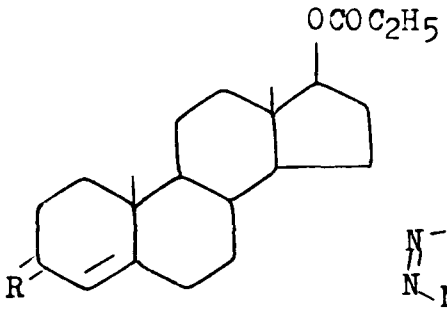
(CLXII)

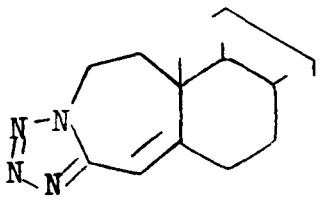


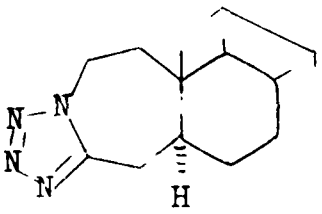
(CLXIII)

Moural and Syhora[65] reported the synthesis of a series of 3-aza-A-homo-4a-eno[3,4-d]tetrazole analogues from the corresponding 3-oxo-4-enosteroids on reaction with hydrazoic acid. The reaction of 3-oxoandrost-4-en-17β-propionate (CLXIV) has been reported to give the tetrazole (CLXVI) which on hydrogenation gave the corresponding dihydro derivative

(CLXVII). The tetrazole (CLXVI) was also obtained when 3-hydroximinoandrost-4-en-17β-propionate (CLXV) was treated with hydrazoic acid. Similarly, 3-oxocholest-4-ene (LXXVIII) was shown to furnish 3-aza-A-homocholest-4a-eno[3,4-d]tetrazole (CLXVIII).





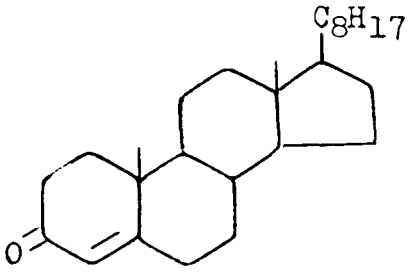


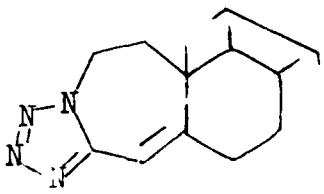
(CLXIV) R, O

(CLXV) R, NOH

(CLXVI)

(CLXVII)

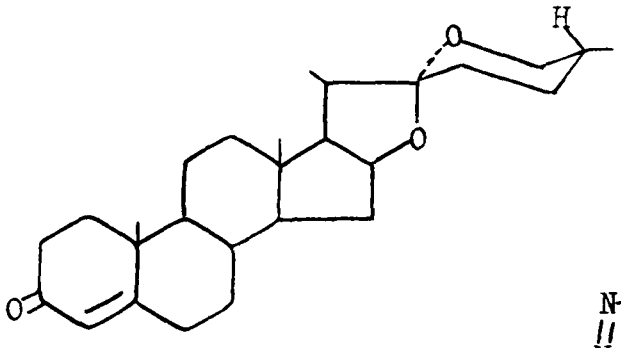




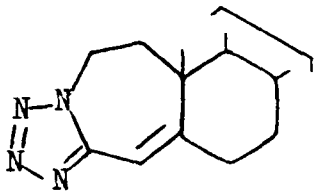
(LXXVIII)

(CLXVIII)

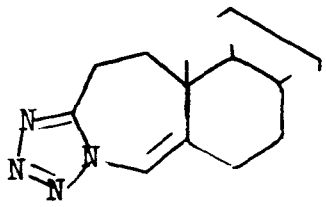
In 1972, a number of ring A, B or D fused steroidal tetrazoles were reported by Singh and coworkers[2b]. Keeping in view the pharmacological effect of the same, Singh et al.[2] treated (25 R)-spirost-4-en-3-one (CLXIX) with an excess of hydrazoic acid in the presence of boron trifluoride etherate and reported the formation of 3-aza-[3,4-d]tetrazoles suchas (CLXX-a) rather than the alternative 4-aza-isomer (CLXX-b). This was done on the basis of spectral characteristics and the observation that Schmidt reaction of 4-en-3-ones or Beckmann rearrangement of their oximes generally yield lactams corresponding to 3-aza-A-homo-4a-en-4-one system[1].



(CLXIX)



(CLXX-a)



(CLXX-b)

Survey of the literature reveals that in the recent past various steroidal tetrazoles have been reported by different authors. The spectral characteristics of a number of steroidal tetrazoles are tabulated below (Table - I).

TABLE - I

Spectral data of some tetrazolo steroids

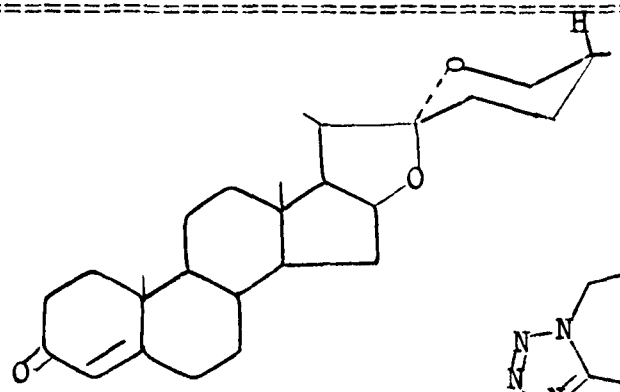
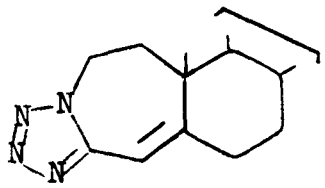
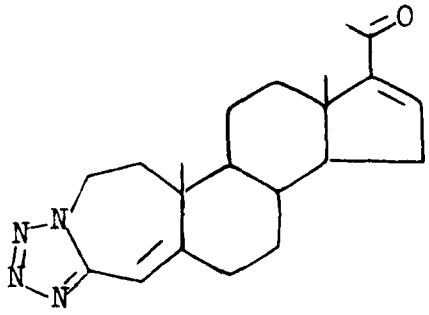
Starting compound(s)	Product(s)	NMR(δ) and IR(cm^{-1})	UV nm(log ε)	Ref.
 (CLXIX)	 (CLXX-a)	6.49s(C_{4a}-H), 4.50m (C_2-H_2), 1.27s(C_{10}-Me) 1650(C=C), 1530, 1450, 1380(C=N, N=N)	243(4.23)	66
 (CLXXI)		6.50s(C_{4a}-H), 4.50m (C_2-H_2), 1660(C=O), 1520, 1445, 1375(C=N, N=N)	242(4.41)	66

Table - I Contd.

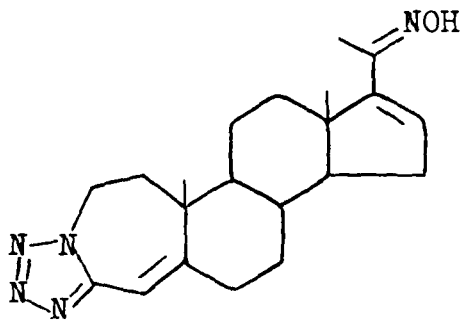
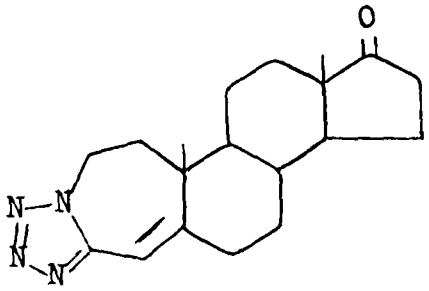
Starting compound(s)	Product(s)	NMR(δ) and IR(cm^{-1})	UV nm(log ε)	Ref.
	 (CLXXII)	6.51s(C_{4a}-H), 4.51m (C_2-H_2); 1648(C=C), 1530, 1445, 1375(C=N, N=N)	240(4.17)	66
	 (CLXXIII)	6.50s(C_{4a}-H), 4.50m (C_2-H_2); 1650(C=C), 1530, 1445, 1385(C=N, N=N)	242(4.23)	66

Table - I Contd.

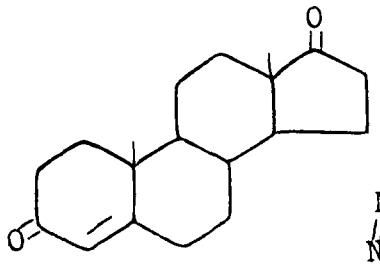
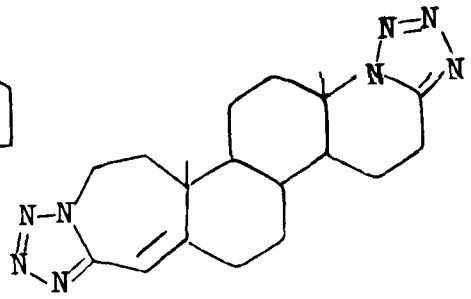
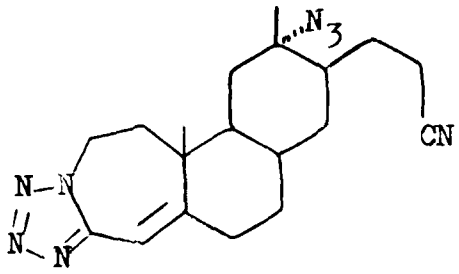
Starting compound(s)	Products(s)	NMR(δ) and IR(cm^{-1})	UV nm(log ε)	Ref.
	 (CLXXIV)  (CLXXV)	6.58s(C_{4a}-H), 4.55m (C_2-H_2), 3.0m(C_{16}-H_2); 1650(C=C), 1530, 1450 (C=N, N=N)	242(4.25)	67,68
	 (CLXXVI)	6.57s(C_{4a}-H), 4.56m (C_2-H_2), 2.49m(NC-C_{16}-H_2); 2250(CN), 2095(N_3), 1650 (C=C), 1530, 1450(C=N, N=N)	242(4.23)	67,68

Table - I Contd.

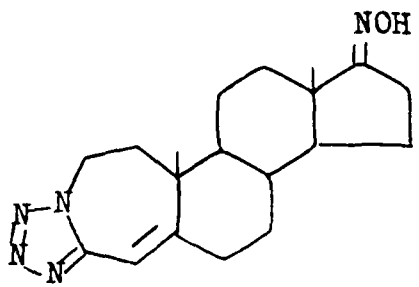
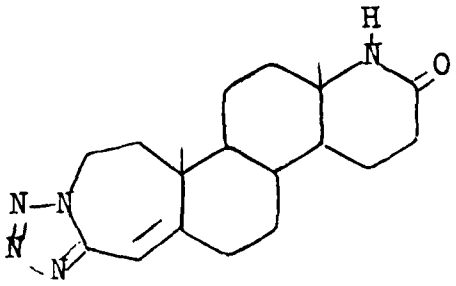
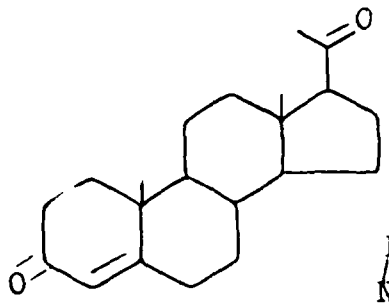
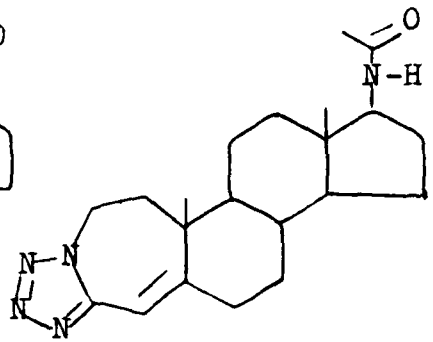
Starting compound(s)	Product(s)	NMR(δ) and IR(cm^{-1})	UV nm(log ε)	Ref.
 (CLXXVII)	 (CLXXVIII)	6.50s(C_{4a}-H), 4.50m (C_2-H_2), 3450, 3125 (NH), 1660(CONH), 1650(C=C), 1530, 1450, 1384(C=N, N=N)	240(4.21)	69
 (CLXXIX)	 (CLXXX)	6.50s(C_{4a}-H), 4.48m (C_2-H_2), 3.92m(C_{17}-αH), 1.97(S), (-NH-CO-Me) 3335(NH), 1670(CONH), 1650(C=C), 1530, 1450, 1375(C=N, N=N)	243(4.22)	70

Table - I Contd.

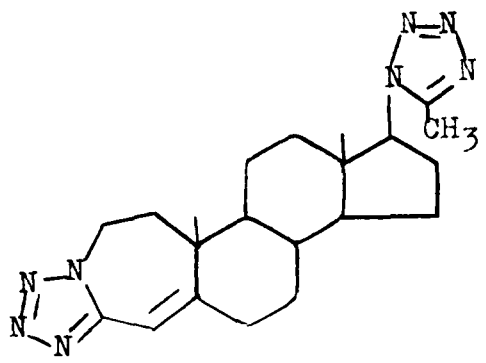
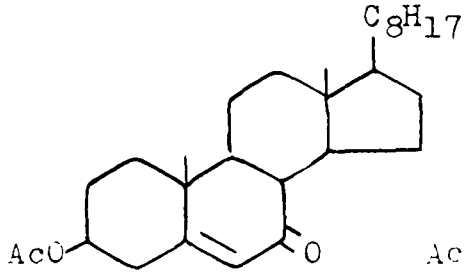
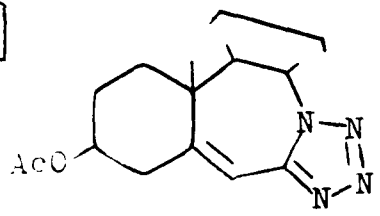
Starting compound(s)	Product(s)	NMR(δ) and IR(cm^{-1})	UV nm(log ε)	Ref.
	 (CLXXXI)	6.51s(C_{4a}-H), 4.50m(C_2-H_2), 4.15m(C_{17}-αH), 2.54s(CH_3-C=N); 1650(C=C), 1520, 1450, 1390 (C=N, N=N)	243(4.23)	70
	 (CIV)  (CLXXXII)	6.62s(C_6-H), 4.75m(C_3-αH), 4.25m(C_8-βH), 2.05s(CH_3-COO); 1735(CH_3-COO), 1665(C=C), 1505, 1465, 1370(C=N, N=N)	241(4.00)	70

Table - I Contd.

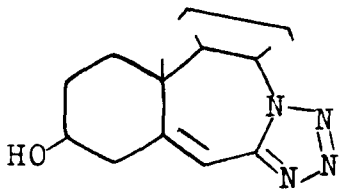
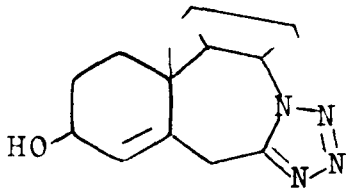
Starting compound(s)	Product(s)	NMR(δ) and IR(cm^{-1})	UV nm(log ε)	Ref.
	 (CLXXXIII)	6.63s(C_6-H), 3.75m(C_3-αH), 4.25m(C_8-βH), 2.12br(OH); (D_2O exchangeable); 3310br(OH), 1663(C=C), 1510, 1465, 1380, 1373 (C=N, N=N)	245(4.06)	70
	 (CLXXXIV)	5.68d(C_4-H; J=2.5 Hz), 4.35m(C_8-βH), 4.02m (C_3-αH), 3.7br(C_6-H_2); 3360br(OH), 1530, 1465, 1389, 1370(C=N, N=N)	-	70

Table - I Contd.

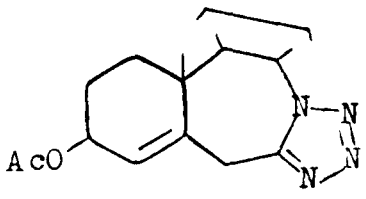
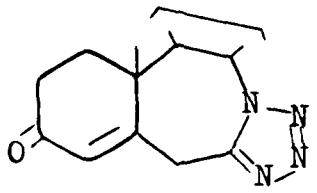
Starting compound(s)	Product(s)	NMR(δ) and IR(cm^{-1})	UV nm(log ε)	Ref.
	 (CLXXV)	5.63d(C_4-H, J=3.3 Hz), 5.03m (C_3-αH), 4.38m(C_8-βH), 3.72br(C_6-H_2), 2.03s (CH_3-COO); 1735(CH_3COO), 1530, 1460, 1380, 1370, (C=N, N=N), 1245(Acetate)	-	70
	 (CLXXXVI)	5.89s(C_4-H), 4.55(C_8-βH), 4.05br(C_6-H_2), 1.17s (C_{10}-Me), 0.83s(C_{13}-Me); 1675(C=C-C=O-), 1625(C=C), 1530, 1462, 1387(C=N,N=N)	235(4.14)	70

Table - I Contd.

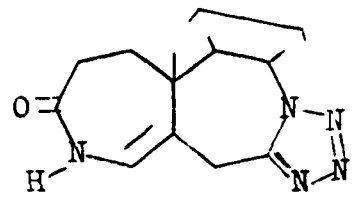
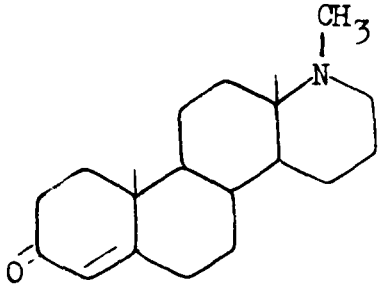
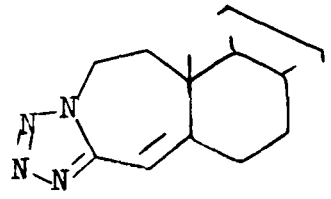
Starting compound(s)	Product(s)	NMR(δ) and IR(cm^{-1})	UV nm(log ε)	Ref.
(CLXXXVI)	 (CLXXXVII)	7.17d(NH; D_2O exchangeable), 5.18d(C_{4a}-H; J=6 Hz), 4.45m(C_8-βH), 3.68br(C_6-H_2); 3226, 3111 (NH), 1667(CONH), 1536, 1460, 1418, 1379(C=N,N=N)	246(4.09)	71
 (CLXXXVIII)	 (CLXXXIX)	6.52s(C_{4a}-H), 4.50m(C_2-H_2), 2.19s(N-CH_3); 1652(C=C), 1528, 1440, 1320(C=N,N=N)	243(4.22)	72

Table - I Contd.

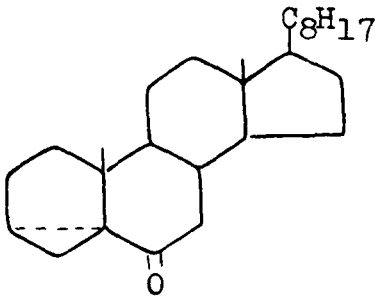
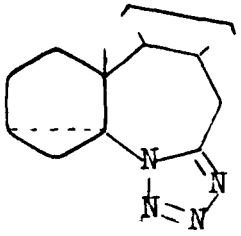
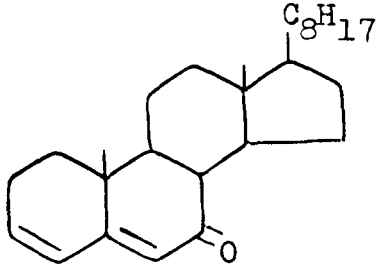
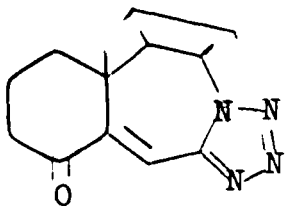
Starting compound(s)	Product(s)	NMR(δ) and IR(cm^{-1})	UV nm(log ε)	Ref.
 (XXXVIII)	 (CXC)	3.36(C_{7a}-H_2), 0.96s (C_{10}-Me), 0.66s(C_{13}-Me); 3030(cyclopropane), 1525, 1460, 1365(C=N, N=N)	-	73
 (CXVIII)	 (CXCI)	7.53s(C_6-H), 4.5br(C_8-βH), 2.5m(C_3-H_2); 1650(C=C-C=O), 1500, 1465, 1380(C=N, N=N)	-	73

Table - I Contd.

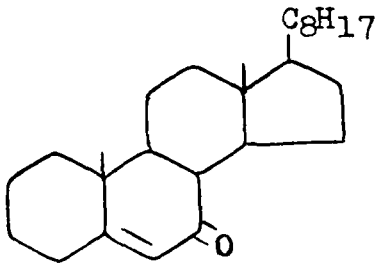
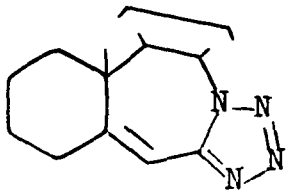
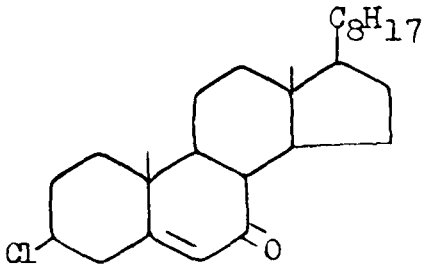
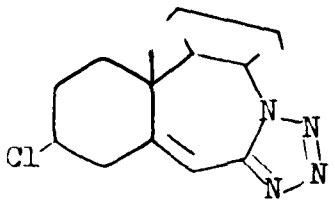
Starting compound(s)	Product(s)	NMR(δ) and IR(cm^{-1})	UV nm(log ε)	Ref.
 (CV)	 (CXCII)	6.55s(C_6-H), 4.22br ($N-C_8$-H), 1670(C=C), 1505, 1465, 1380 (C=N, N=N)	243(4.10)	73
 (CXCIII)	 (CXCIV)	6.63s(C_6-H), 4.21br ($N-C_8$-H), 3.81br(C_3-αH), 1660(C=C), 1505, 1470, 1380(C=N, N=N)	240(4.13)	73

Table - I Contd.

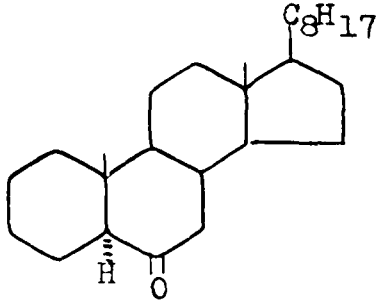
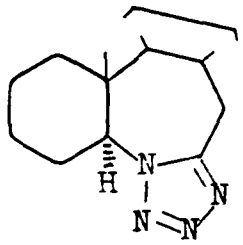
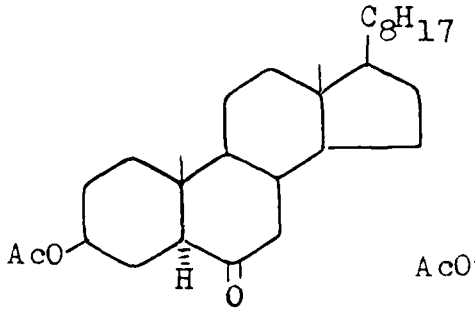
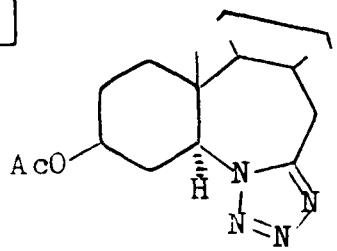
Starting compound(s)	Product(s)	NMR(δ) and IR(cm^{-1})	UV nm(log ε)	Ref.
 (XXVI)	 (CXCV)	4.2dd(C_5-αH ; JC_5-αH, C_4-βH = 10 Hz , C_5-αH, C_4-αH = 7 Hz), 3.21d(C_{7a}-Hx; JC_{7a}-Hx; C_{7a}-Hy = 15 Hz); 0.93s(C_{10}-Me), 0.90, 0.81, 0.63(remaining methyls); 1540, 1460, 1380(C=N, N=N)	-	74
 (XXXIV)	 (CXCVI)	4.78br(C_3-αH), 4.45dd(C_5-αH; J = 14 and 7 Hz), 3.4d(C_{7a}-H; J = 15 Hz), 2.06s(CH_3COO); 0.55s(C_{13}-CH_3), 0.91, 0.83, 0.65(methyls); 1720(CH_3COO), 1525, 1455, 1360(C=N, N=N)		74

Table - I Contd.

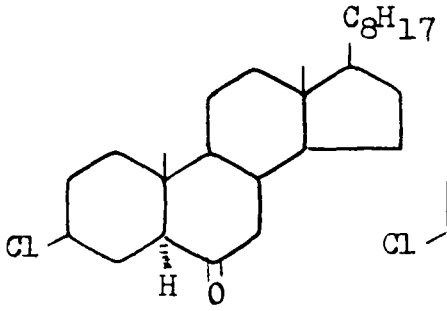
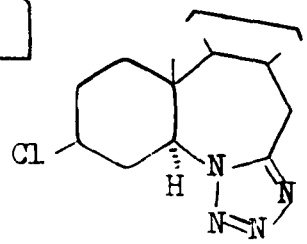
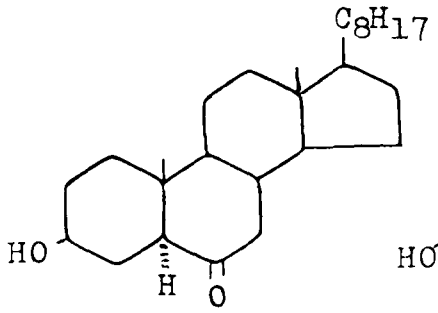
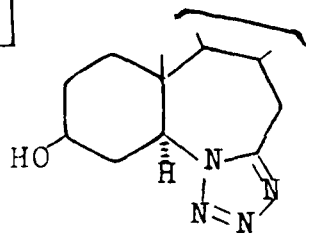
Starting compound(s)	Product(s)	NMR(δ) and IR(cm^{-1})	UV nm(log ε)	Ref.
 (CXCVII)	 (CXCVIII)	4.66 dist.dd(C_5-αH and C_3-αH; J = 10 and 6 Hz), 3.4d(C_{7a}-H; J = 15 Hz), 0.53s(C_{13}-CH_3), 0.93 0.83, 0.66(methyls); 1540, 1470, 1380(C=N, N=N)	-	74
 (CXCIX)	 (CC)	4.33dd(C_5-αH; J = 12 and 7 Hz), 3.75br(C_3-αH), 3.38d(C_{7a}-H; J = 15 Hz), 0.52s(C_{13}-CH_3); 0.91, 0.81, 0.63(methyls); 3400br(OH), 1540, 1480, 1390(C=N, N=N)	-	74

Table - I Contd.

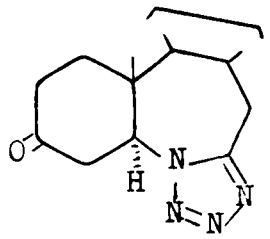
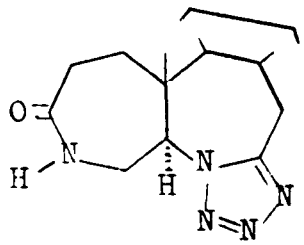
Starting compound(s)	Product(s)	NMR(δ) and IR(cm^{-1})	UV nm(log ε)	Ref.
	 (CCI)	4.66(C_5-αH; J = 13 and 6 Hz), 3.5(C_{7a}-H_2), 0.68s(C_{13}-CH_3), 0.91, 0.81, 0.73(methyls); 1722(C=O), 1530, 1460, 1360 (C=N, N=N)	-	74
	 (CCII)	7.0br(NH, D_2O exchangeable), 4.66br(C_5-αH), 4.06(C_{4a}-H_2), 3.41m(C_{7a}-H_2), 0.45s(C_{13}-CH_3), 0.91, 0.81, 0.65(methyls); 3340, 3200(NH), 1690, 1640 (CONH), 1540, 1470, 1380 (C=N, N=N)	-	74

Table - I Contd.

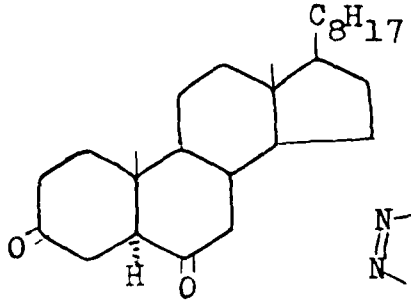
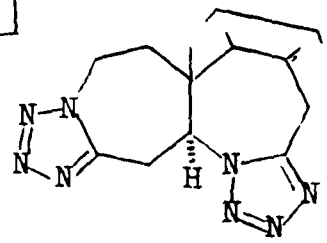
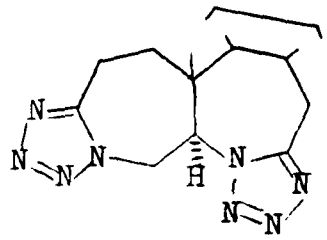
Starting compound(s)	Product(s)	NMR(δ) and IR(cm^{-1})	UV nm(log ε)	Ref
 (LXXIV)	 (CCIII)	4.93d(C_5-α½H; J = 7 Hz), 4.48m (C_5-α½H, C_2-H, C_{4a}-Heq), 4.0d (C_{4a}-H_{ax}; J = 10Hz), 3.36d (C_{7a}-H; J = 15Hz); 1535, 1465, 1380(C=N, N=N)	-	75
 (CCIV)		5.48 dist.d(C_5-αH; J_{aa}= 10Hz; J_{ae}= 6Hz), 5.0d(C_{4a}-H_2, major, J = 10Hz), 3.55d(C_{7a}-H, J = 15Hz), 3.13m(C_2-H_2); 1540, 1470, 1390 (C=N, N=N)	-	75

Table - I Contd.

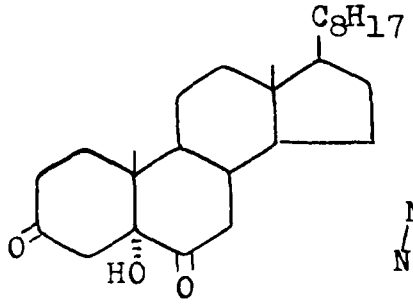
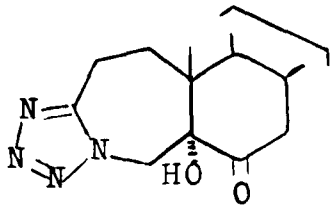
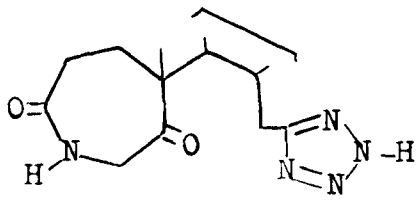
Starting compound(s)	Product(s)	NMR(δ) and IR(cm^{-1})	UV nm(log ε)	Ref.
	 (CCV)  (CCVI)	5.05 and 4.41d(C_{4a}-H_2; J = 16Hz), 3.25m(C_2-H_2); 3400, 3200br(OH), 1715(C=O), 1545, 1480, 1390 (C=N, N=N)	-	75
	 (CCVII)	6.8br(CONH), 4.63m(C_5-H_2), 3.3br(C_7-H_2), 2.3m(C_2-H_2), 1.1(C_{10}-CH_3), 0.88, 0.80, 0.63 (methyls); 3350, 3340(NH of tetrazole), 3260br(NH of lactam), 1750(C=O), 1630(CONH), 1570, 1480, 1390(C=N, N=N)	-	75

Table - I Contd.

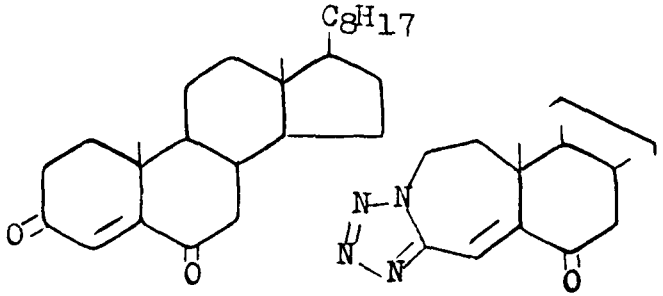
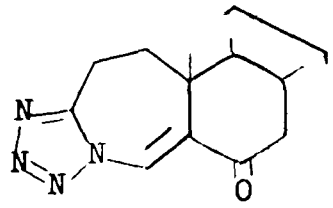
Starting compound(s)	Product(s)	NMR(δ) and IR(cm^{-1})	UV nm(log ε)	Ref.
(CXII)	 (CCVIII)	7.13s(C_{4a}-H), 4.56m(C_2-H_2) 1690(C=C-C=O), 1520, 1460, 1380(C=N, N=N)	260(4.38)	75
	(CCIX) 	7.8s(C_{4a}-H), 3.2m(C_2-H_2); 1690(C=C-C=O), 1620(C=C), 1520, 1455, 1380(C=N, N=N)	243(4.1)	75

Table - I Contd.

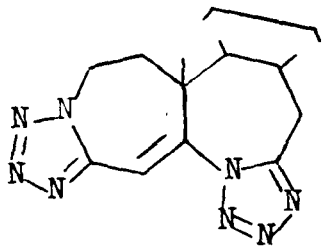
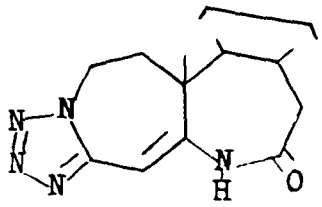
Starting compound(s)	Product(s)	NMR(δ) and IR(cm^{-1})	UV nm(log ε)	Ref.
	 (CCX)	7.03s(C_{4a}-H), 4.68m(C_2-H_2), 3.45d(C_{7a}-H, J = 15Hz); 3060w(C=C-H), 1670s(C=C), 1530, 1460, 1375(C=N, N=N)	245(4.4)	75
	 (CCXI)	8.56br s(CONH), 6.8s(C_{4a}-H), 4.58m(C_2-H_2); 3220(NH), 1675, 1655(CONH), 1640(C=C), 1530, 1455, 1375(C=N, N=N)	243(4.1)	75

Table - I Contd.

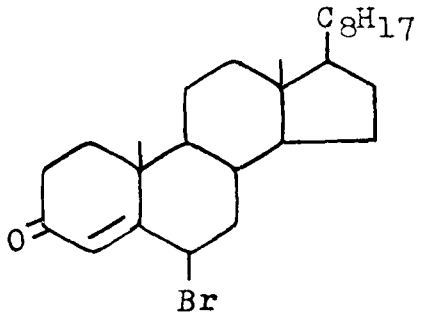
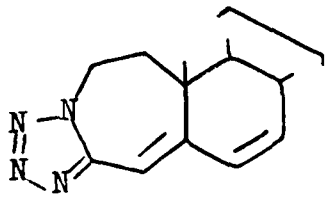
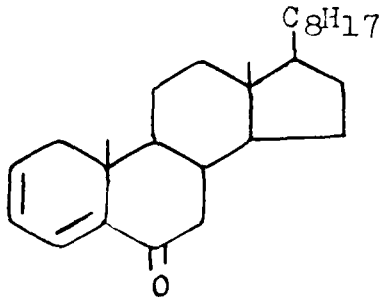
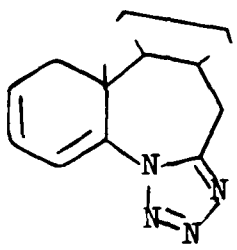
Starting compound(s)	Product(s)	NMR(δ) and IR(cm^{-1})	UV nm(log ε)	Ref.
 (XCII)	 (CCXII)	6.36s(C_{4a}-H), 6.03m(C_6-H and C_7-H), 4.51m(C_2-H_2); 1650(C=C), 1537, 1475, 1390(C=N, N=N)	287(4.47)	75
 (CXI)	 (CCXIII)	6.05m(3H-C_2-H, C_3-H and C_4-H), 3.24d(C_{7a}-H; J = 15Hz), 0.9s(C_{10}-Me), 0.7(C_{13}-Me); 1650(C=C), 1550, 1510, 1460, 1375 (C=N, N=N)	280(ε = 10900)	76

Table - I Contd.

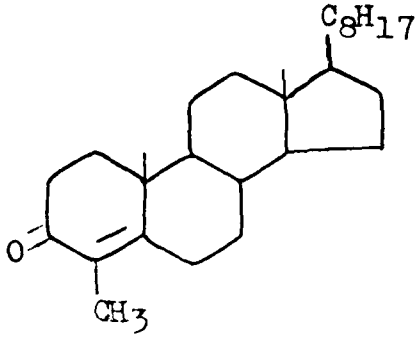
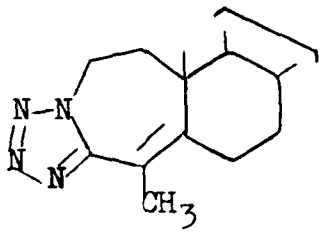
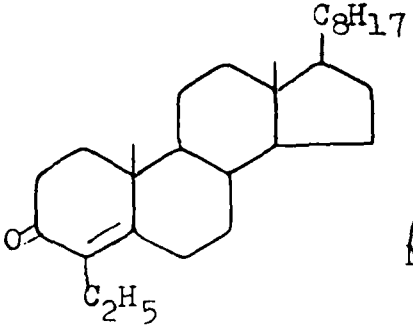
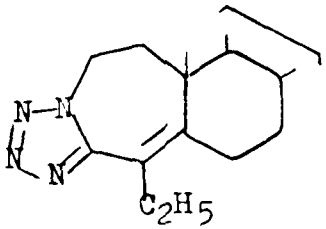
Starting compound(s)	Product(s)	NMR(δ) and IR(cm^{-1})	UV nm(log ε)	Ref.
 (CCXIV)	 (CCXV)	4.35m(C_2-H_2), 2.13s(C_{4a}-CH_3), 0.98, 0.88(methyls); 1600(C=C), 1510, 1450, 1375(C=N, N=N)	-	77
 (CCXVI)	 (CCXVII)	4.39m(C_2-H_2), 0.95, 0.85 (methyls); 1600(C=C), 1510, 1450, 1380(C=N, N=N)	-	77

Table - I Contd.

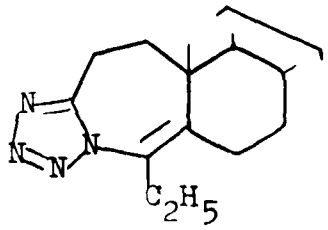
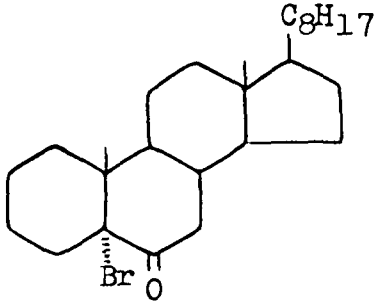
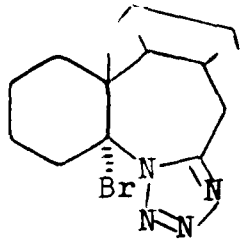
Starting compound(s)	Product(s)	NMR(δ) and IR(cm^{-1})	UV nm(log ε)	Ref.
	 (CCXVIII)	2.89m(C_2-H_2), 0.9, 0.8(methyls), 1630(C=C), 1530, 1450, 1370 (C=N, N=N)	-	77
 (LVI)	 (CCXIX)	3.4d(C_{7a}-H; J = 15Hz), 0.9s (C_{10}-Me), 0.71s(C_{13}-Me), 0.83, 0.80(methyls); 1537(C=N), 1470, 1370(N=N), 700(C-Br)	-	78

Table - I Contd.

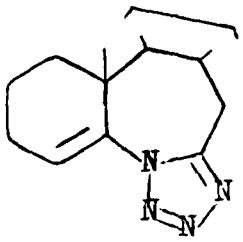
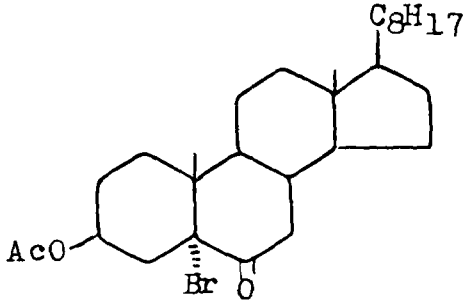
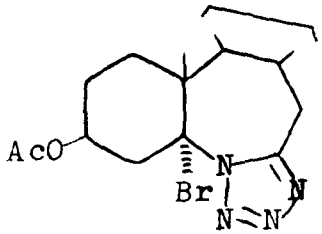
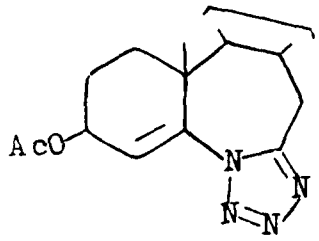
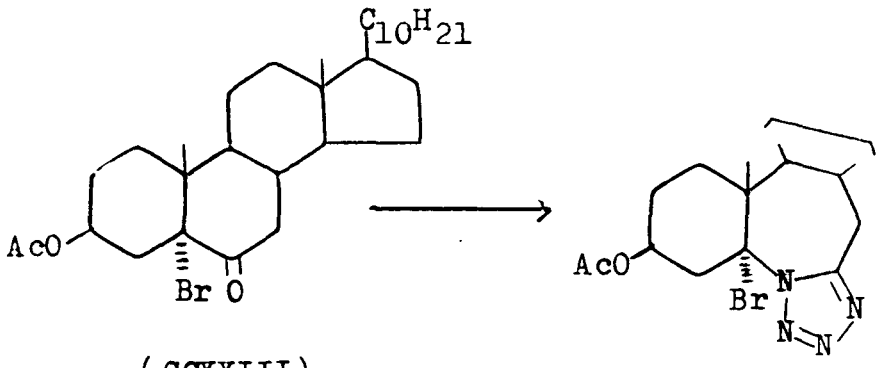
Starting compound(s)	Product(s)	NMR(δ) and IR(cm^{-1})	UV nm(log ε)	Ref.
	 (CCXX)	6.06t(C_4-H), 3.35d(C_{7a}-H; J = 15Hz), 0.92s(C_{10}-Me), 0.45(C_{13}-Me), 0.63, 0.81 (methyls); 1650(C=C), 1520 (C=N), 1465, 1385(N=N)	-	78
 (LIV)	 (CCXXI)	5.3br(C_3-αH, $W_{\frac{1}{2}}$ = 16Hz), 3.4d(C_{7a}-H, J = 15Hz), 2.03s (CH_3-COO), 0.93(C_{10}-Me), 0.66 (C_{13}-Me), 0.83, 0.76(methyls); 1725(CH_3-COO), 1520(C=N), 1435, 1360(N=N)	-	78

Table - I Contd.

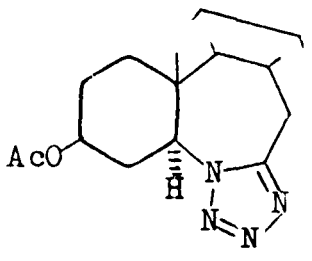
Starting compound(s)	Product(s)	NMR(δ) and IR(cm^{-1})	UV nm(log ε)	Ref.
	 (CCXXII)	6.1d(C_4-H; J = 3Hz), 5.58br (C_3-αH; $W_{\frac{1}{2}}$ = 12Hz), 3.4br,d (C_{7a}-H; J = 15Hz), 2.11s (CH_3-COO), 0.9(C_{10}-Me), 0.7 (C_{13}-Me), 0.8, 0.75(methyls); 1730(CH_3COO), 1642(C=C), 1510 (C=N), 1460, 1370(N=N)	-	78

Recently, a number of steroidal tetrazoles of stigmastane series have also been reported[79,80]. The steroidal ketones used for this purpose were 3β-acetoxy-5α-bromostigmastan-6-one (CCXXIII), stigmastane-3,6-dione (CCXXVI), 3α-5-cyclo-5α-stigmastan-6-one (CCXXVIII), 3β-hydroxy-5α-stigmastan-6-one (CCXXX), its 3β-chloro (CCXXXI) analogue, stigmast-5-en-7-one (CXLI), its 3β-hydroxy (CCXXXV), 3β-chloro (CXLII) and 3β-acetoxy (CCXXXVI) analogues;

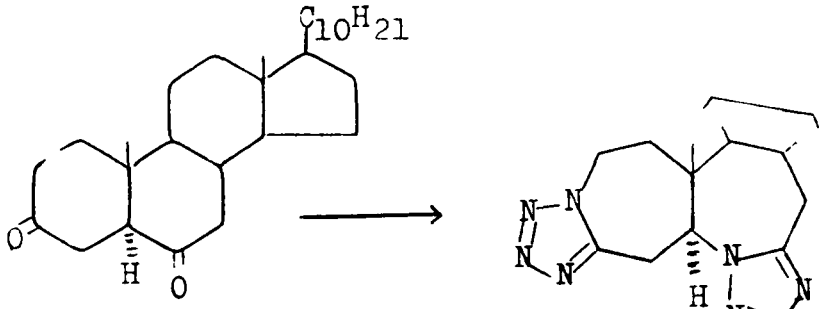


(CCXXIII) (CCXXIV)

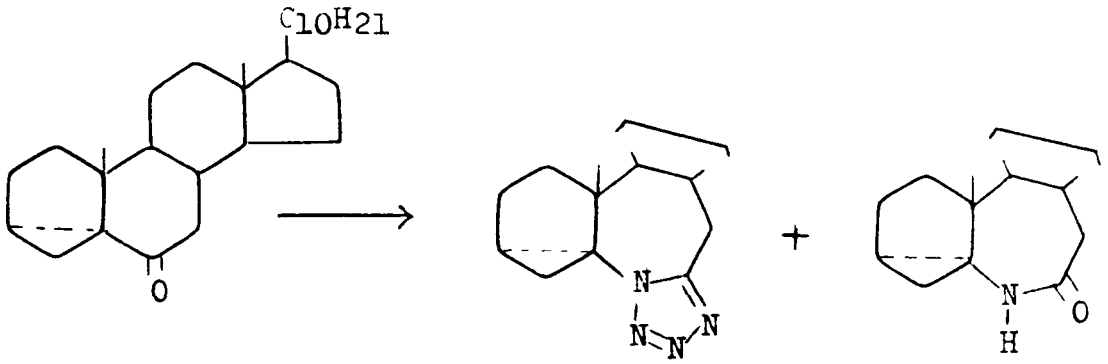
(CCXXIV) Na/Amyl alcohol



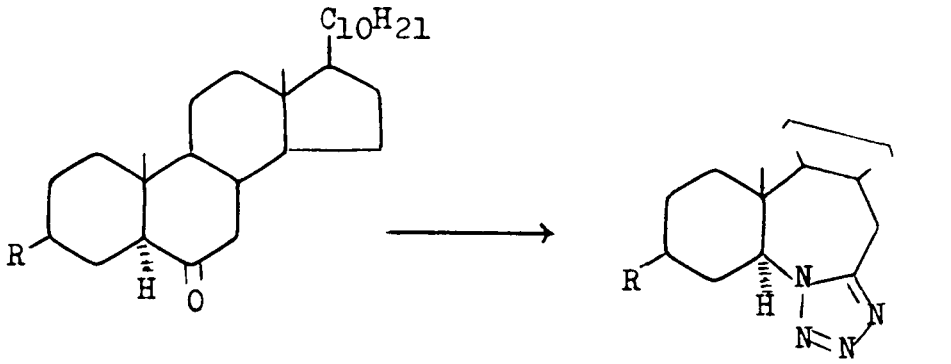
(CCXXV)



(CCXXVI) (CCXXVII)

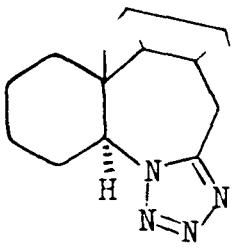


(CCXXVIII) (CCXXIX) (CXXXVI)



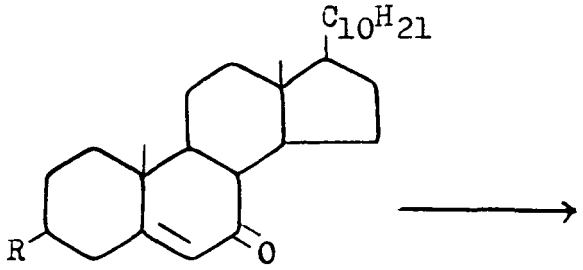
(CXXX) R, OH (CCXXXII) R, OH

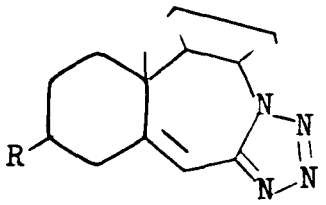
(CCXXXI) R, Cl (CCXXXIII) R, Cl

(CCXXXIII) $\xrightarrow{Na/Amylalcohol}$ 

(CCXXXIV)

(CCXXXII) $\xrightarrow{Ac_2O/Py.}$ (CCXXV)





(CXLI)	R, H	(CCXXXVII)	R, H
(CCXXXV)	R, OH	(CCXXXVIII)	R, OH
(CXLII)	R, Cl	(CCXXXIX)	R, Cl
(CCXXXVI)	R, OAc	(CCXL)	R, OAc

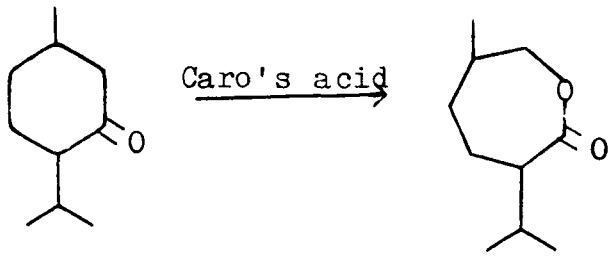
PART - III

OXASTEROIDS

Oxasteroids constitute a class of modified steroids where an oxygen atom is incorporated into one of carbocyclic rings of the steroidal frame work. Oxasteroids have been recognised as an important class of compounds due to their manifold biological activities and their formation as intermediates in many reactions. Several naturally occurring oxasteroids were found to display a diverse variety of biological activity and this stimulated extensive research in oxygen containing steroids. As intermediates they became important for the insertion of labelled oxygen into the steroidal nucleus, ring contraction, preparation of methyl derivative, etc.

Oxasteroids have been synthesized in wide variety of ways but the most elegant method is the time honoured, Baeyer-Villiger oxidation of steroidal ketones. Although more than three quarters of a century has passed since Baeyer-Villiger oxidation[81] has been discovered, it still remains to be the method of choice. Baeyer-Villiger oxidation is in fact the transformation of carbonyl compounds into esters or lactones by peroxy compounds. In 1899, Baeyer-Villiger[81] noted that cyclic ketones like menthone (CCXLI), camphor etc. when

treated with permonosulphuric acid (Caro's acid) gave the corresponding lactones of ω-hydroxyacid, e.g. menthone (CCXLI) gave the lactone (CCXLII).



(CCXLI) (CCXLII)

Later other peroxyacids were also found capable of bringing about this oxidation. Hydrogen peroxide in acidic or alkaline solution or in the presence of a suitable catalyst was found to oxidise ketones in this manner.

Hassall[82] and Smith[83] have given a thorough review on the mechanism, stereochemistry, kinetics, migratory aptitute of groups, electronic and steric effects and effect of per-acid's concentration in Baeyer-Villiger oxidation.

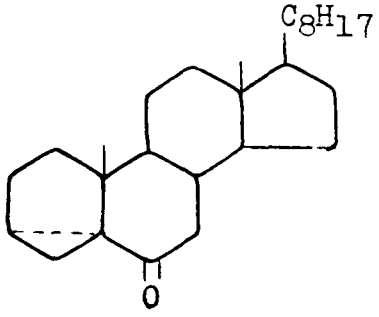
Baeyer-Villiger Oxidation of Steroidal Ketones

Both saturated as well as α,β-unsaturated steroidal ketones have been subjected to Baeyer-villiger oxidation in order to prepare oxasteroids. Since it will not be possible to encompass total work done in this field, only the oxasteroids

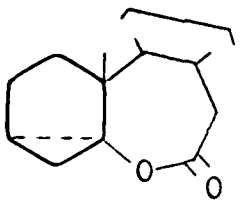
prepared from these laboratories will be elaborated.

Saturated Ketones

A number of saturated steroidal ketones, particularly 6-oxosteroids have been subjected to peracid oxidation and in most of the cases lactones are formed as the major product. The Baeyer-Villiger oxidationsof 3α,5-cyclo-5α-cholestan-6-one (XXXVIII) and its 3β-chloro (CXCVII), 3β-bromo (XXXIX) and 3β-iodo (CCXLIII) derivatives were studied[84]. The ketone (XXXVIII) on treatment with perebenzoic acid gave a single lactone, 6-oxa-B-homo-3α,5-cyclo-5α-cholestan-7-one (CCXLIV).

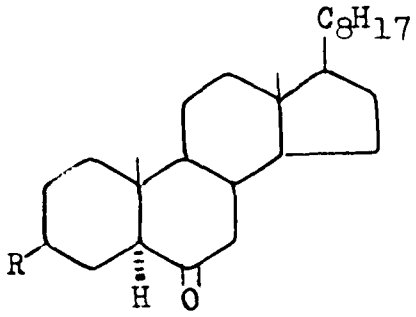


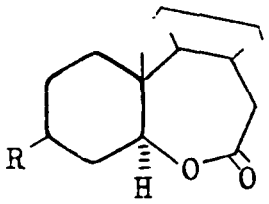
(XXXVIII)

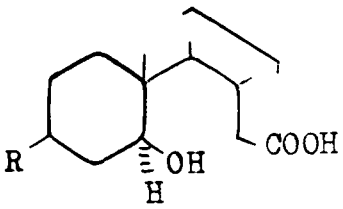


(CCXLIV)

Similar oxidation of (CXCVII) provided the lactone 3β-chloro-6-oxa-B-homo-5α-cholestan-7-one (CCXLV) and the secoacid, 3β-chloro-5β-hydroxy-5,6-secocholestan-6-oic acid (CCXLVI). The ketones (XXXIX) and (CCXLIII) were shown to give single lactones, 3β-bromo-6-oxa-B-homo-5α-cholestan-7-one (CCXLVII) and 3β-iodo-6-oxa-B-homo-5α-cholestan-7-one (CCXLVIII), respectively.



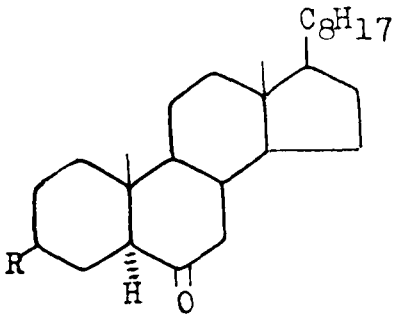


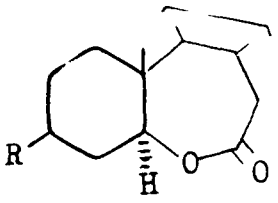


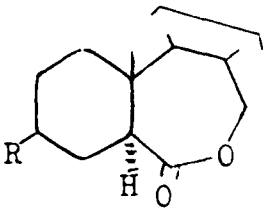
(CXCVII)	R, Cl	(CCXLV)	R, Cl		
(XXXIX)	R, Br	(CCXLVII)	R, Br	(CCXLVI)	R, Cl
(CCXLIII)	R, I	(CCXLVIII)	R, I		

Structural assignment were based upon spectral and chemical properties. In earlier observations also Baeyer-Villiger oxidation of 6-ketosteroids stereospecifically gave the 6-oxasteroids by preferential migration of a more substituted C_5 relative to C_7[85].

It has however been recently reported[86] that the steroidal 6-ketones, 3β-acetoxy-5α-cholestan-6-one (XXXIV), its 3β-hydroxy (CXCIX) and 3β-chloro (CXCVII) analogues as well as 5α-cholestan-6-one (XXVI) yielded correspondingly a mixture of 6-oxa (CCXLIX, CCL, CCXLV, CCLI) and 7-oxa (CCLII, CCLIII, CCLIV, CCLV) isomers in contradiction to the earlier observation[85]. This shows that the migratory aptitude of C_5 and C_7 are comparable.

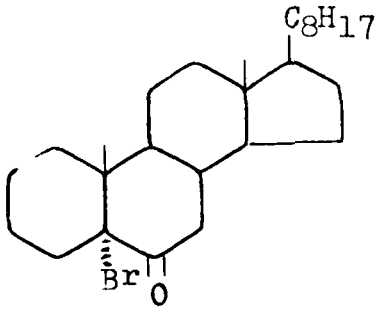




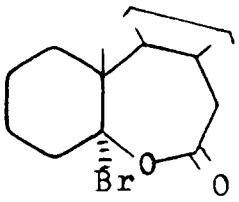


(XXXIV)	R, OAc	(CCXLIX)	R, OAc	(CCLII)	R, OAc
(CXCIX)	R, OH	(CCL)	R, OH	(CCLIII)	R, OH
(CXCVII)	R, Cl	(CCXLV)	R, Cl	(CCLIV)	R, Cl
(XXVI)	R, H	(CCLI)	R, H	(CCLV)	R, H

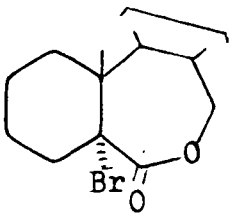
Ahmad et al.[32,87] carried out the Baeyer-Villiger oxidation of 5α-bromocholestan-6-one (LVI) and its 3β-acetoxy (LIV) analogue using perbenzoic acid as the oxidising agent and p-toleunesulphonic acid as the catalyst. The aim was to investigate the effect of substituents in close vicinity of ketonic function on the course of the reaction. The ketone (LVI) gave isomeric lactones, 6-oxa-B-homo-5-bromo-5α-cholestan-7-one (CCLVI) and 7-oxa-B-homo-5α-bromocholestan-6-one (CCLVII) and a rearranged product, 7-bromo-6-oxa-B-homocholestan-4-en-7-one (CCLVIII).



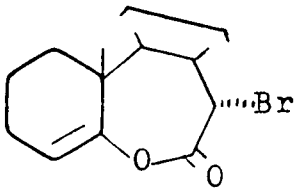
(LVI)



(CCLVI)



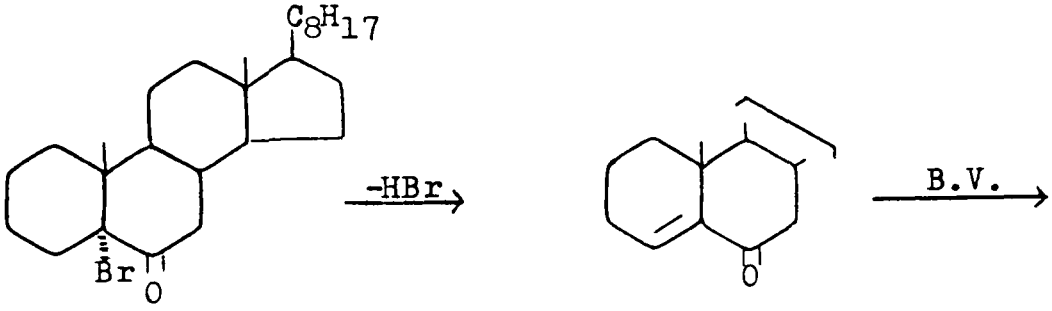
(CCLVII)



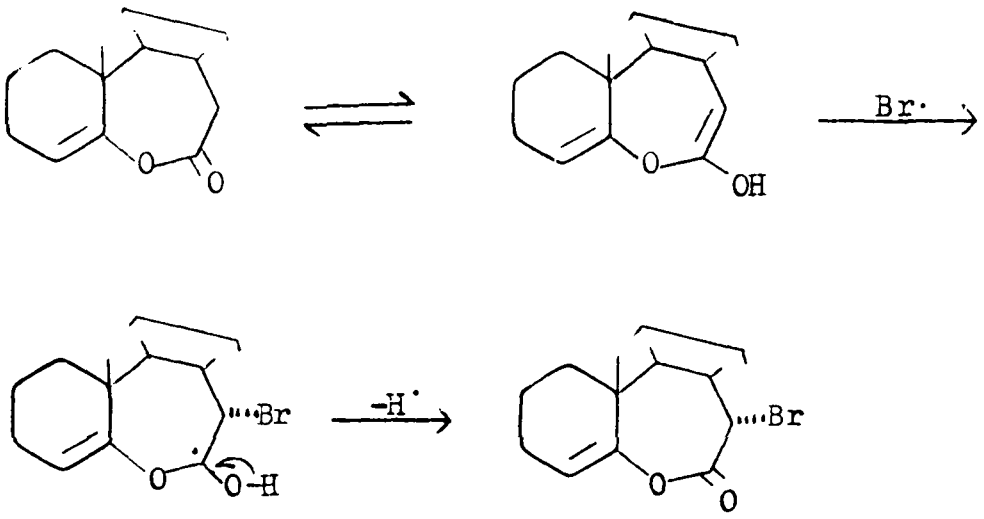
(CCLVIII)

A tentative mechanism involving the attack of bromine radical at one stage, was proposed for the conversion of (LVI) to (CCLVIII) as shown in Scheme - I.

SCHEME - I



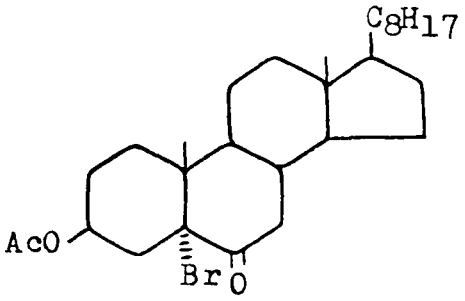
(XLII)



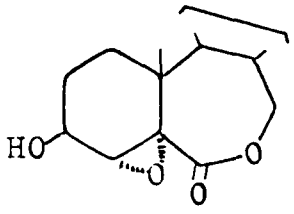
(CCLVIII)

The peroxide (Ph-CO-O-CO-Ph) present in the reaction mixture may initiate the α-bromination by bromine radical, the latter coming from HBr.

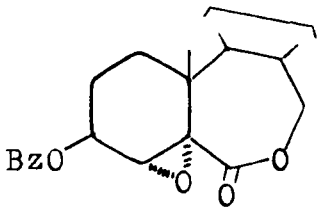
3β-Acetoxy-5α-bromocholestan-6-one (LIV) on Baeyer-Villiger oxidation provided 3β-hydroxy-4α,5-epoxy-7-oxa-B-homo-5α-cholestan-6-one (CCLIX) and its 3β-benzoate (CCLX) analogue as well as 3β-hydroxy-5-bromo-7-oxa-B-homo-5α-cholestan-6-one (CCLXI).



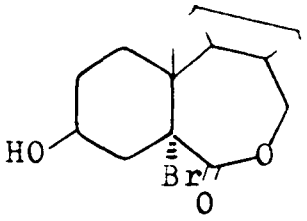
(LIV)



(CCLIX)

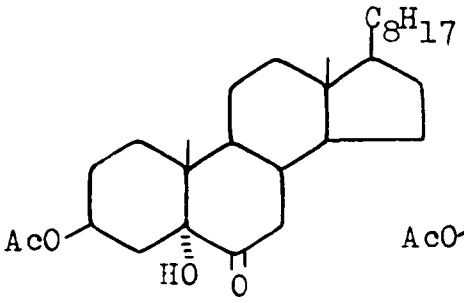


(CCLX)

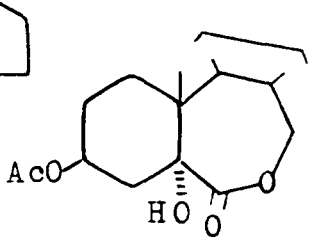


(CCLXI)

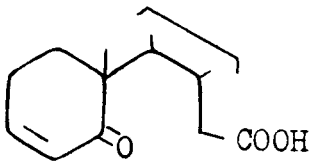
A similar study of 5α-hydroxy substituted 6-keto steroids, namely 3β-acetoxy-5-hydroxy-5α-cholestan-6-one (CCLXII) and its 3β-chloro (CCLXV) analogue was also made[88]. The ketone (CCLXII) under the reaction conditions afforded 3β-acetoxy-5-hydroxy-7-oxa-B-homo-5α-cholestan-6-one (CCLXIII) and 5-keto-5,6-secocholest-3-en-6-oic acid (CCLXIV).



(CCLXII)

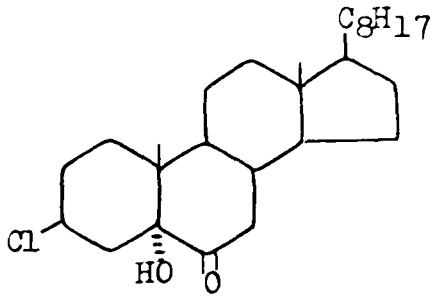


(CCLXIII)

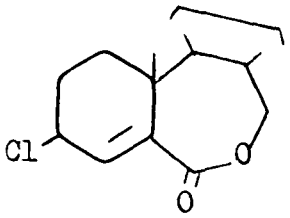


(CCLXIV)

Similarly the perbenzoic acid oxidation of the ketone (CCLXV) furnished 3β-chloro-7-oxa-B-homocholest-4-en-6-one (CCLXVI) and the secoketo acid (CCLXIV)

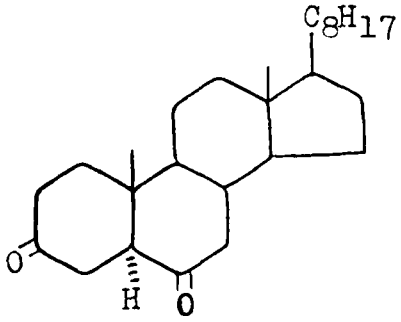


(CCLXV)

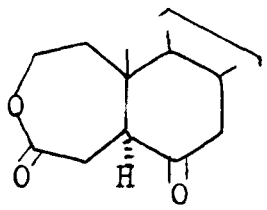


(CCLXVI)

5α-Cholestane-3,6-dione (LXXIV) on similar treatment with varying concentration of perbenzoic acid invariably afforded 3-oxa-A-homo-5α-cholestane-4,6-dione (CCLXVII)[89].



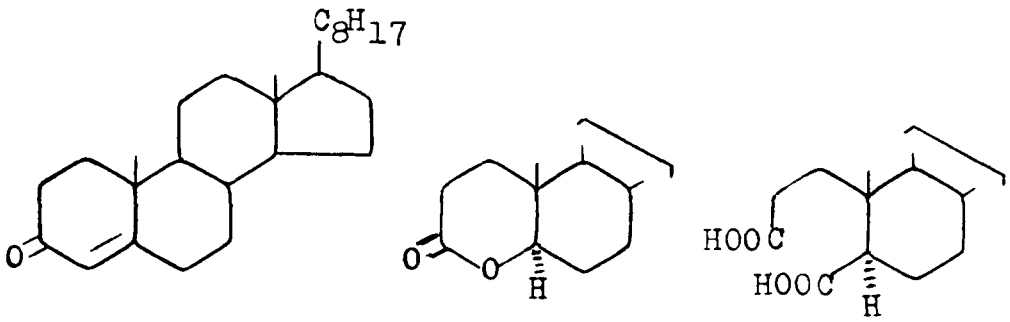
(LXXIV)



(CCLXVII)

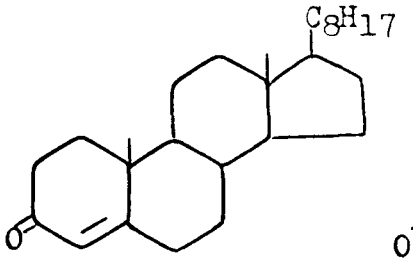
α,β-Unsaturated Ketones

In 1941, Salamon[90] observed that oxidation of cholest-4-en-3-one (LXXVIII) with potassium persulphate and sulphuric acid yielded a neutral compound (CCLXVIII) and an unidentified acid. In 1950, Turner[91] repeated Salamon's experiments and identified the neutral product as 4-oxa-5α-cholestan-3-one (CCLXVIII) and the acid as dihydro Diels' acid (CCLXIX).

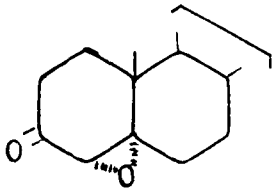


(LXXVIII) (CCLXVIII) (CCLXIX)

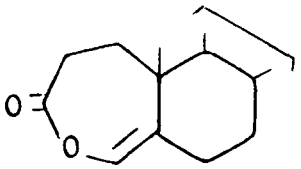
Pinhey and Schaffner[92], in continuation of their previous study[93] oxidised (LXXVIII) with perbenzoic acid in the presence of catalytic amounts of anhydrous perchloric acid and reported the isolation of 4α,5-epoxy-5α-cholestan-3-one (CCLXX), 4-oxa-A-homocholest-4a-en-3-one (CCLXXI), 5-formyl-4-oxa-5α-cholestan-3-one (CCLXXII) and 3,5-seco-4-norcholestan-5-one-2-carboxylic acid (CCLXXIII).



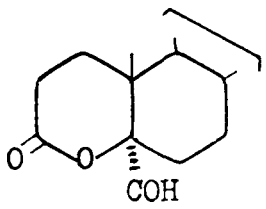
(LXXVIII)



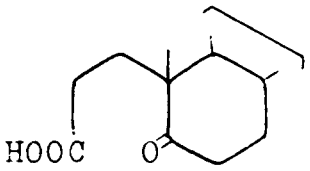
(CCLXX)



(CCLXXI)

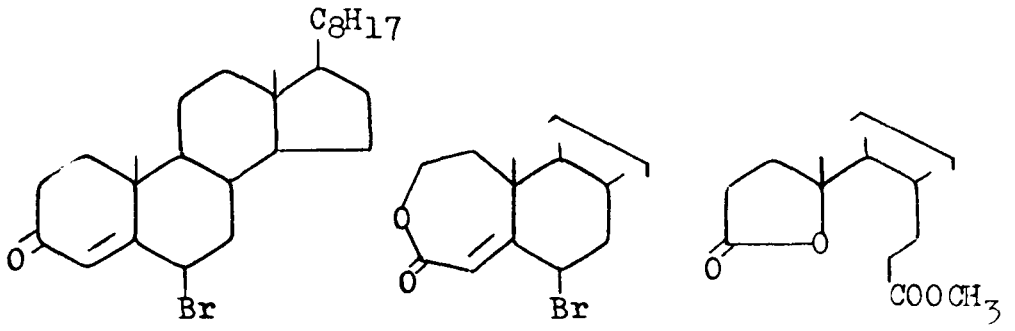


(CCLXXII)



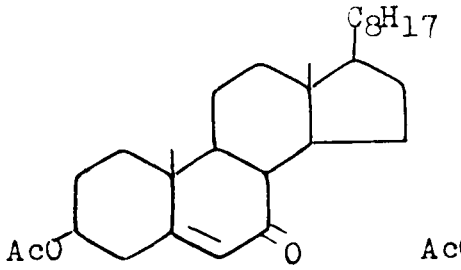
(CCLXXIII)

Ahmad et al.[94] subjected 6β-bromocholest-4-en-3-one (XCII) to perbenzoic acid oxidation using p-toluenesulphonic acid as catalyst. The choice of the substrate (XCII) was governed by the desire to know the effect of a substituent in close vicinity of 4-en-3-one moiety on the course of the reaction and product distribution. The products obtained were 6β-bromo-3-oxa-A-homocholest-4a-en-4-one (CCLXXIV), a product of primary oxidation and the γ-lactone methyl ester (CCLXXV), a product of extended reaction.

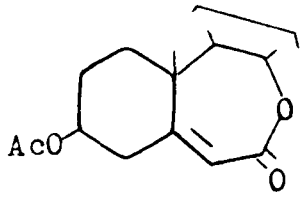


(XCII) (CCLXXIV) (CCLXXV)

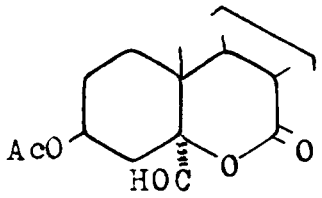
In view of the absence of any analogous study of the peracid oxidation of 5-en-7-ones relative to 4-en-3-ones. Ahmad et al.[95] attempted the Baeyer-Villiger oxidation of 3β-acetoxycholest-5-en-7-one (CIV) and cholest-5-en-7-one (CV). The ketone (CIV) on oxidation, with perbenzoic acid as oxidant and p-toluenesulphonic acid monohydrate as catalyst, afforded 3β-acetoxy-7a-oxa-B-homocholest-5-en-7-one (CCLXXVI), 3β-acetoxy-6-oxa-5-formyl-5β-cholestan-7-one (CCLXXVII) and a mixture of the seco acids, 3β-acetoxy-5-keto-5,7-seco-6-norcholestan-7-oic acid (CCLXXVIII) and 5-keto-5,7-seco-6-norcholest-3-en-7-oic acid (CCLXXIX).



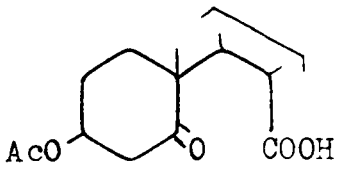
(CIV)



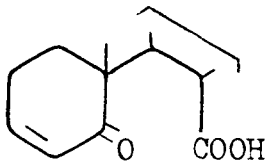
(CCLXXVI)



(CCLXXVII)

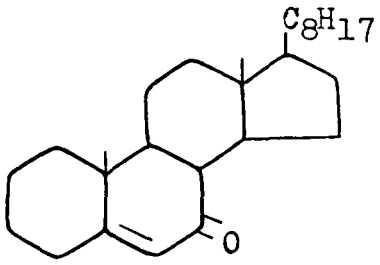


(CCLXXVIII)

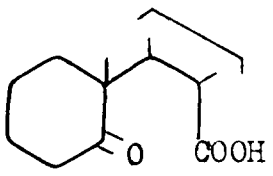


(CCLXXIX)

Oxidation of cholest-5-en-7-one (CV) under similar conditions furnished a single compound, 5-keto-5,7-seco-6-norcholestan-7-oic acid (CCLXXX).

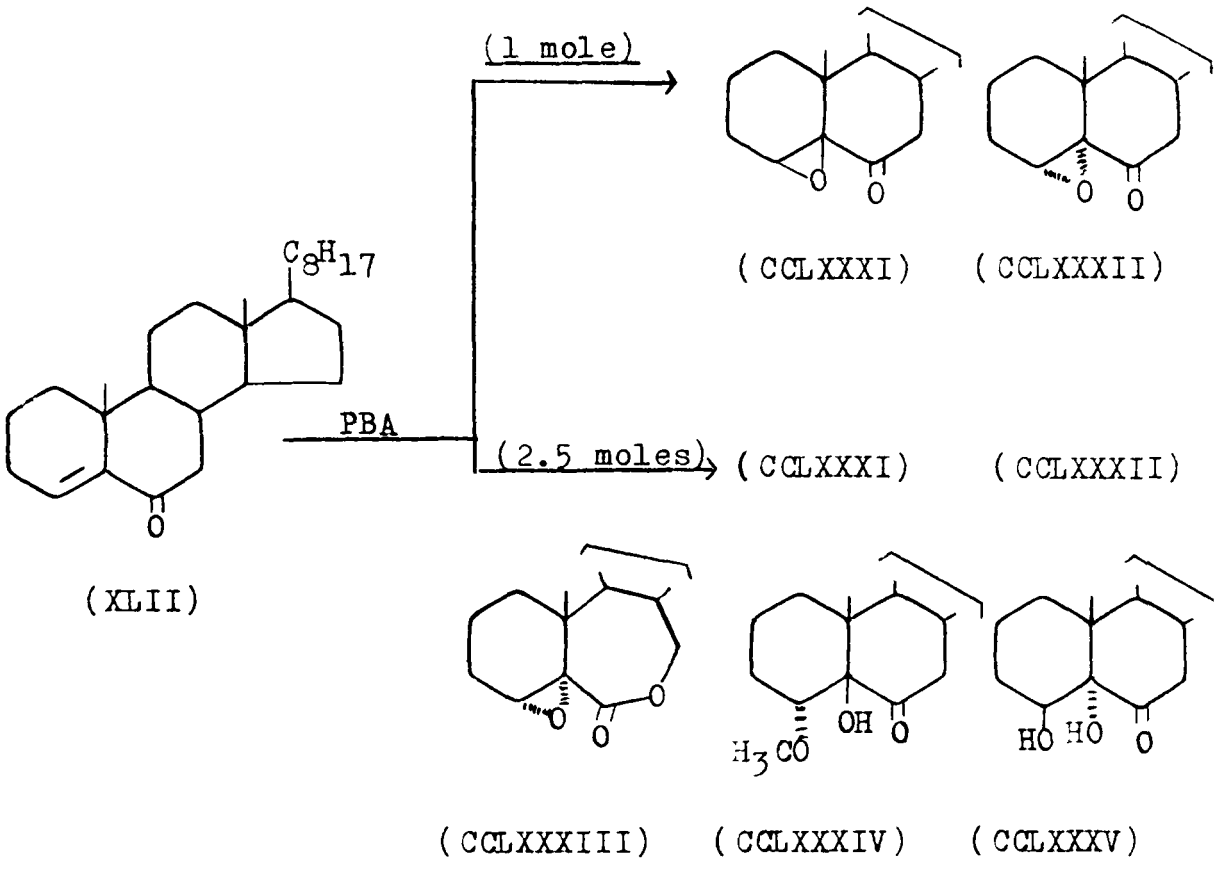


(CV)

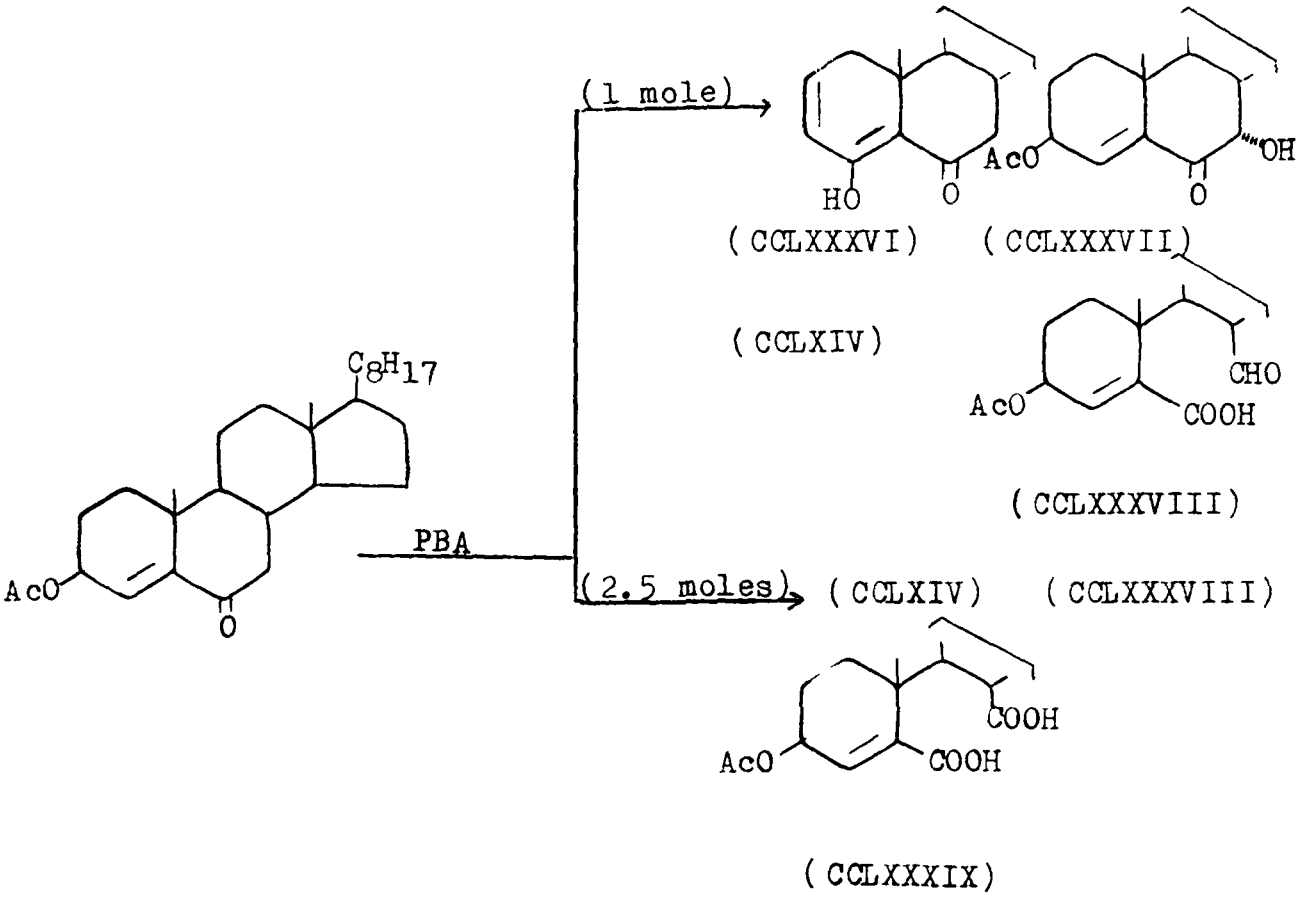


(CCLXXX)

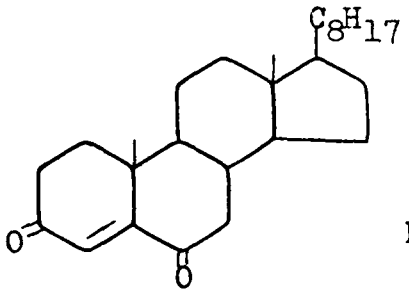
The Baeyer-Villiger oxidation of cholest-4-en-6-one (XLII)[96] with one mole equivalent of perbenzoic acid using p-toluenesulphonic acid as catalyst afforded 4β,5-oxido-5β-cholestan-6-one (CCLXXXI) and 4α,5-oxido-5α-cholestan-6-one (CCLXXXII). On treatment with an excess of perbenzoic acid (2.5 moles) the ketone (XLII) furnished (CCLXXXI), (CCLXXXII) and 4α,5-oxido-7-oxa-B-homo-5α-cholestan-6-one (CCLXXXIII) along with 5-hydroxy-4α-methoxy-5β-cholestan-6-one (CCLXXXIV) and 4β,5-dihydroxy-5α-cholestan-6-one (CCLXXXV).



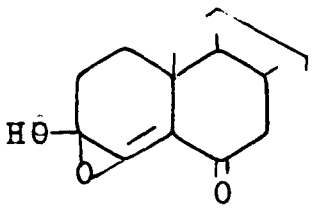
Reaction of 3β-acetoxycholest-4-en-6-one (XCVI) with one mole equivalent of perbenzoic acid has been shown to afford 4-hydroxycholesta-2,4-dien-6-one (CCLXXXIV), 7α-hydroxy-3β-acetoxycholest-4-en-6-one (CCLXXXVII), 5-keto-5,6-seco-cholest-3-en-6-oic acid (CCLXIV) and 3β-acetoxy-6,7-seco-8-formylcholest-4-en-6-oic acid (CCLXXXVIII). With an excess of perbenzoic acid (2.5 moles), the ketone (XCVI) provided (CCLXIV), (CCLXXXVIII) and 3β-acetoxy-6,7-secocholest-4-en-5,8-dicarboxylic acid (CCLXXXIX)[97].



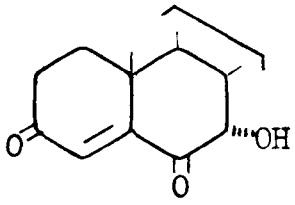
In a very interesting sequence of Baeyer-Villiger oxidation, cholest-4-ene-3,6-dione (CXII) with one mole equivalent of perbenzoic acid, gave 3-hydroxy-3,4-oxidocholest-4-en-6-one (CCXC), 7α-hydroxycholest-4-ene-3,6-dione (CCXCI) and 4-hydroxy-6-methoxycholesta-4,6-dien-3-one (CCXCII). With 2 mole equivalent of perbenzoic acid the same ketone (CXII) afforded (CCXC) and novel lactone, 5,7aα-oxido-6-oxa-B-homo-5α-cholestane-3,7-dione (CCXCIII). With three mole equivalents of perbenzoic acid the ketone (CXII) furnished (CCXCIII) and its product of further oxidation, 5,7aα-oxido-3,6-dioxa-A,B-bishomo-5α-cholestane-4,7-dione (CCXCIV)[98].



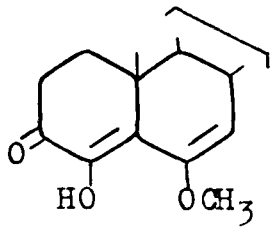
(CXII)



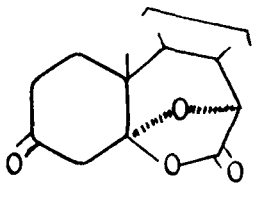
(CCXC)



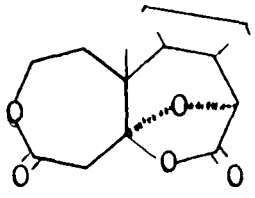
(CCXCI)



(CCXCII)

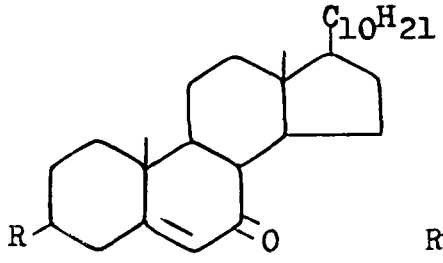


(CCXCIII)



(CCXCIV)

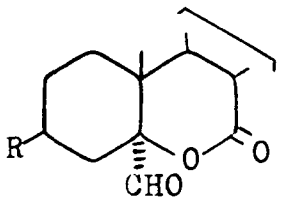
Recently Ahmad et al.[99] reported similar studies on some α,β-unsaturated ketones of the stigmastane series. Reaction of stigmast-5-en-7-one (CXLI) with perbenzoic acid afforded only 5-keto-5,7-seco-6-norstigmastan-7-oic acid (CCXCVII) while its 3β-acetoxy analogue (CCXXXVI) gave 6-oxa-5α-formyl-7-oxostigmastan-3β-yl acetate (CCXCV) and 5-keto-5,7-seco-6-norstigmast-3-en-7-oic acid (CCXCVIII). Similar oxidation of 3β-chlorostigmast-5-en-7-one (CXLII) furnished stigmasta-3,5-dien-7-one (CCXCIX), 6-oxa-5α-formyl-7-oxo-stigmastan-3β-yl chloride (CCXCVI) and seco acid (CCXCVIII).



(CXLI) R, H

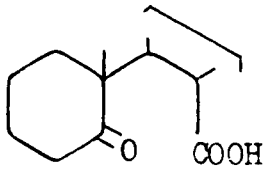
(CCXXXVI) R, OAc

(CXLII) R, Cl

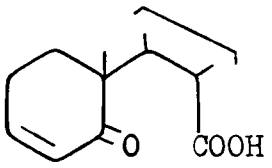


(CCXCV) R, OAc

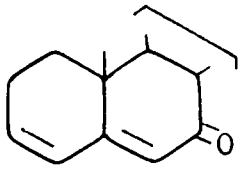
(CCXCVI) R, Cl



(CCXCVII)

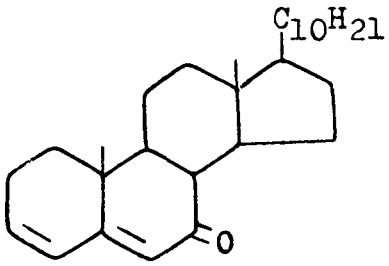


(CCXCVIII)

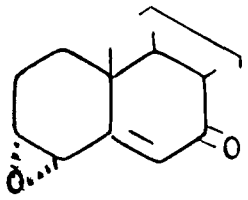


(CCXCIX)

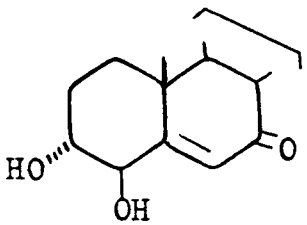
The ketone (CCXCIX) on similar oxidation provided epoxide (CCC), the diol (CCCI) the ε-lactone (CCCII) and 7-oxo-3α,4α-oxido-5α,6β-dihydroxystigmastane (CCCIII).



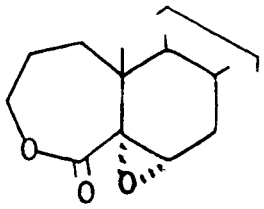
(CCXCIX)



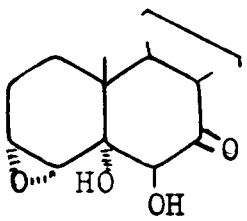
(CCC)



(CCCI)



(CCCII)



(CCCIII)

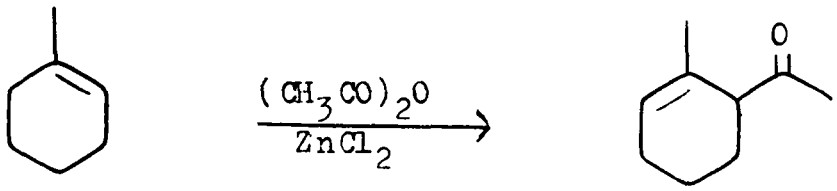
DISCUSSION

PART - I(A)

REACTION OF STEROIDAL OLEFINS WITH ACID ANHYDRIDES AND ZINC CHLORIDE

During Friedel-Crafts' acylation of olefins, the frequent and sometimes exclusive formation of β,γ-unsaturated ketones has been reported[100]. These products, accompanied by isomerization have generally led to more stable α,β-unsaturated system.

The acylation of an olefin is conveniently carried out by reaction in acetic anhydride with zinc chloride catalyst. A seminal discovery was reported by Deno and Chafetz[101] that the reaction of 1-methylcyclohexene (CCCIV) gives exclusively 6-acetyl-1-methylcyclohexene (CCCV).



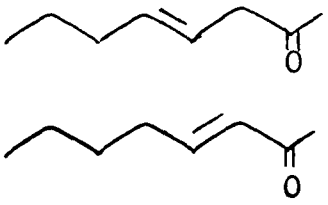
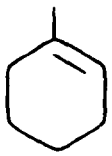
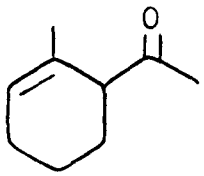
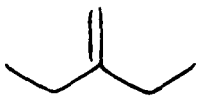
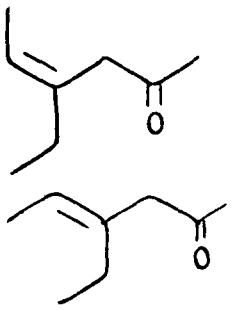
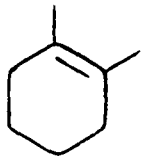
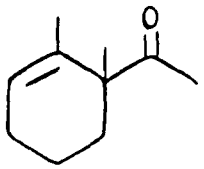
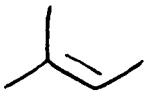
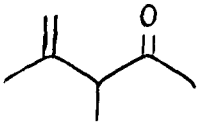
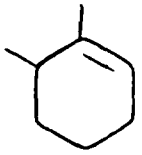
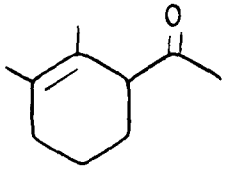
(CCCIV) (CCCV)

Further it has been shown that (CCCV) and related β,γ-unsaturated ketones from other substituted medium ring carbocyclic olefins can be produced in 90% yields[102]. Additions to 1-methyl-4-lakylcyclohexenes give predominantly

the β,γ-unsaturated ketones formed by addition, trans to the substituent[103].

Beak and Berger[104] subjected a number of cyclic and acyclic olefins to the reaction with anhydride and zinc chloride in a suitable solvent at ambient temperature and isolated the corresponding β,γ-unsaturated ketones listed in the Table - II.

TABLE - II

Olefin	Product(s)	Olefin	Product(s)
			
			
			

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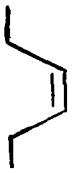
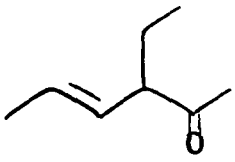
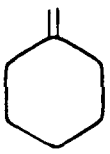
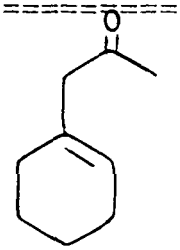
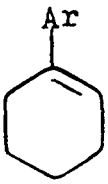
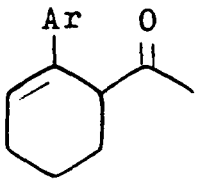
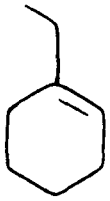
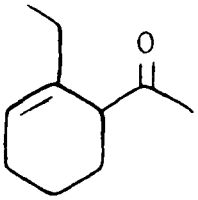
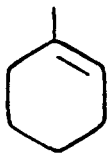
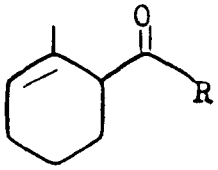
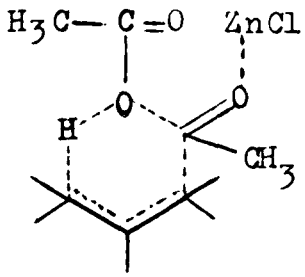
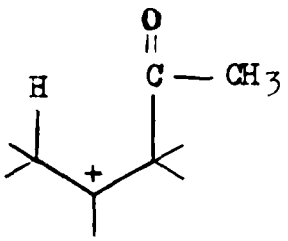
			
			
Ar, C_6H_5 Ar, p-$CH_3OC_6H_4$ Ar, p-BrC_6H_4 Ar, p-$CH_3C_6H_4$ Ar, p-FC_6H_5			
			
R, CH_2CH_3 R, $(CH_2)_2CH_3$			

The exclusive formation of β,γ-unsaturated ketones is explained by Dubois et al.[103] on the basis of transition state (CCCVI) in which electrophilic attack of an acetic anhydride-zinc chloride complex on the double bond is concerted with

the cleavage of the γ-carbon-hydrogen bond.[105]



(CCCVI)



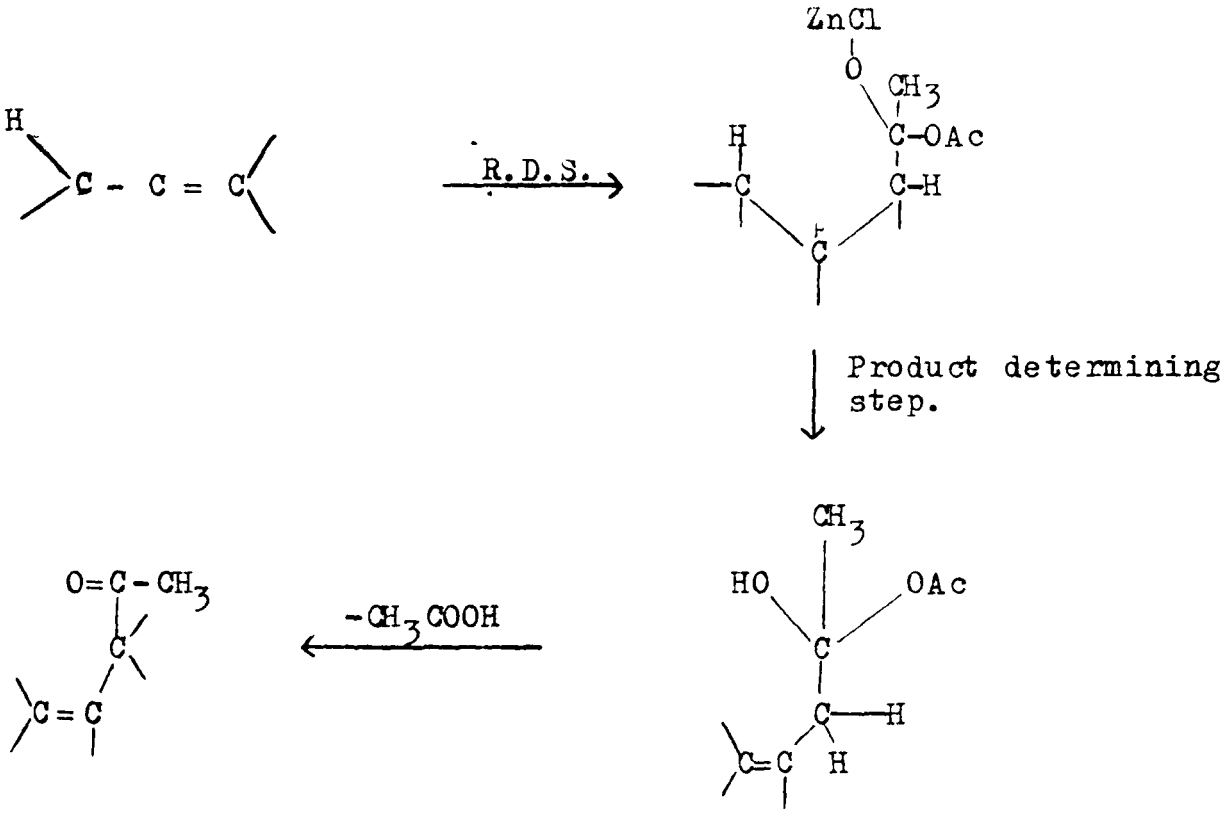
(CCCVII)

Such a mechanism is symmetry-allowed and analogous to the ene-reaction suggested by Hoffmann and Tsushima[106] for the reaction of acetylium ions with olefins.

On the other hand many earlier proposals for the acylation of olefins under similar conditions have been formulated in terms of a carbonium-ion intermediate (CCCVII) on the basis of product and rate studies[100-102,107,108]. Groves and Jones[102] have suggested that an intermediate (CCCVII) produced by axial addition of the acetylium electrophile provides a cation which undergoes stereoelectronically controlled loss of the γ-proton.

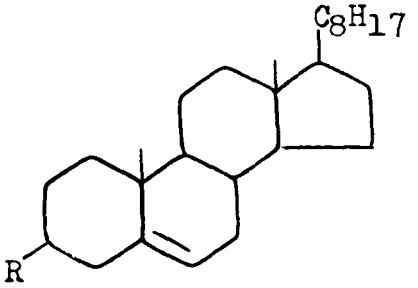
Keeping in view the above observations, Beak et al.[104] suggested that the mechanism of the reaction must involve at least two steps, as shown in Scheme - II on the basis of divergent kinetic and isotope effect studies.

SCHEME - II



It is interesting that the reaction which has been recently formulated as concerted process which would be symmetry-allowed, in fact proceeds by a stepwise mechanism.

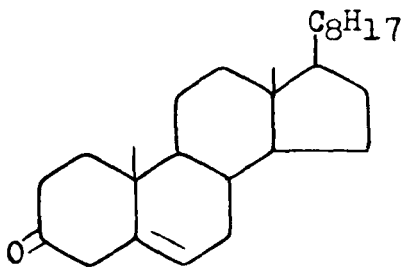
Motivated by the interesting results obtained in this field we have undertaken the synthesis of β,γ-unsaturated ketones in the cholestane series. Steroidal olefins chosen for the present exploratory studies are cholest-5-ene (CCCVIII), its 3β-chloro (CCCIX) and 3β-acetoxy (CCCX) analogues. In addition to these olefins, cholest-5-en-3-one (CCCXI) has also been included for the present study.



R = H (CCCVIII)

R = Cl (CCCIX)

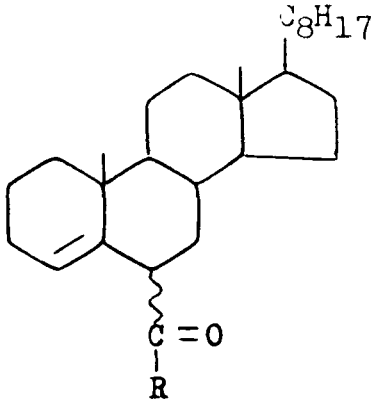
R = OAc (CCCX)



(CCCXI)

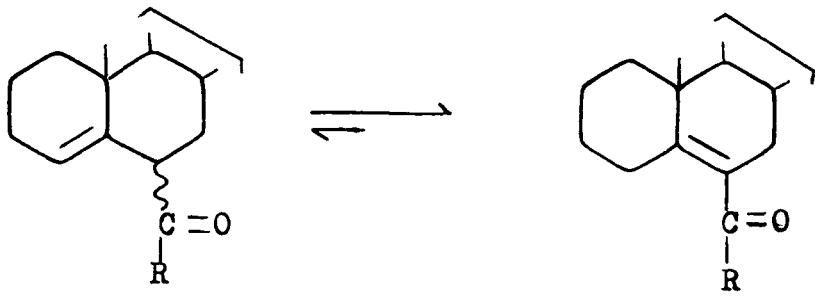
The acylation in all the cases has been carried out by acetic anhydride and propionic anhydride in the presence of dry zinc chloride as catalyst at 0-5° under complete anhydrous conditions. The products obtained have been characterized on the basis of chemical and spectral evidences.

The products of the reaction of cholest-5-ene (CCCVIII) and acetic anhydride and propionic anhydride are likely to have the gross structure (A).



(A) R, CH_3 , R, C_2H_5

Such a structure is prone to isomerization in two ways. Being a β,γ-unsaturated ketone (A) can isomerize to (B) under alkaline or acidic conditions,to give the corresponding α,β-unsaturated ketone, a relatively more stable system.

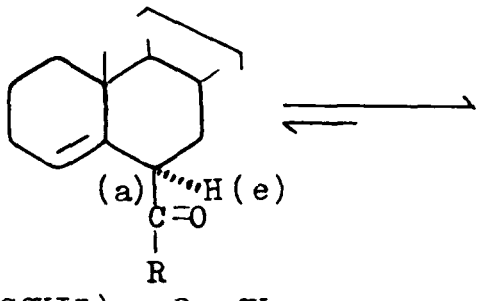


(A) (B)

(CCCXIV) R, CH_3

(CCCXX) R, C_2H_5

Assuming the group RCO- to be axial (β-oriented), it can change over to a relatively more stable equatorial position (α-oriented) under alkaline or acidic conditions.



(CCCXII) R, CH_3 (CCCXIII) R, CH_3

(CCCXVIII) R, C_2H_5 (CCCXIX) R, C_2H_5

From the subsequent discussions it became obvious that all these expectations were realized thus making interpretations in few cases a bit more difficult.

The mechanism of the reaction of an acid anhydride and an olefin in the presence of zinc chloride has been the subject matter of several papers[cf 104]. In view of its complexity it is reasonable to believe that the incoming group RCO- at C_6 may occupy axial (thermodynamically less stable) position. Subsequent to this, the substituents at C_6 (RCO-) may isomerize to the more favourable equatorial position either during the course of the reaction or after designed isomerization.

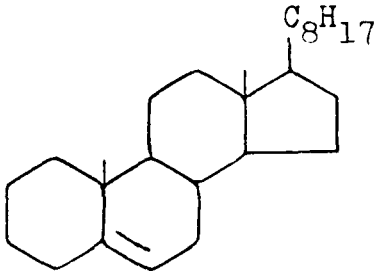
It is interesting to record that the NMR signal for C_4-vinylic proton varies substantially depending upon the disposition of the C_6 substituents. When the substituent at C_6 is axial (β-oriented) the C_4-vinylic proton appears at about δ 5.5 [in cholest-4-ene the C_4-vinylic proton appears at about δ 5.22 in the 100 MHz spectrum of an authentic sample]. On the other hand the C_4-vinylic proton shifts up field to about δ.4.8 when the same substituent occupies equatorial position (α-oriented). This observation, though not substantiated fully, can be of some use in the determination of the stereochemistry of the substituents at C_6 in cholest-4-ene system.

The systems studied, however, do not seem to give consistent results as was expected. Needless to say, the variationsin results may be due to a number of factors and further work in this area may eventually be required.

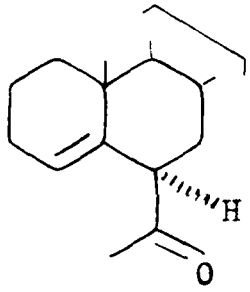
Reaction of Cholest-5-ene (CCCVIII) with Acetic anhydride and Zinc chloride : 6α-Acetylcholest-4-ene (CCCXIII)

Cholest-5-ene (CCCVIII) was submitted to Friedel-Crafts' acylation using acetic anhydride and dry zinc chloride where olefin, anhydride and zinc chloride portions were maintained at 2:20:1. Usual work up and column chromatography over silica gel provided a single crystalline product, m.p. 126°, which

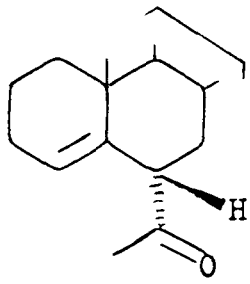
analysed for $C_{29}H_{48}O$.



(CCCVIII)



(CCCXII)



(CCCXIII)

The IR spectrum of the compound exhibited absorption bands at 1705 and 1650 cm^{-1}. The sharp band at 1705 was due to the exocyclic carbonyl chromophore (C=O) whereas the medium band at 1650 cm^{-1} could easily be assigned to the C=C stretching frequency. Therefore, the molecular composition and IR spectral values suggested the presence of an acetyl moiety (CH_3CO) in the compound and hence two isomeric structures (CCCXII) and (CCCXIII) could be formulated. A clear distinction between these two isomers was made possible with the help of its more informative NMR spectrum.

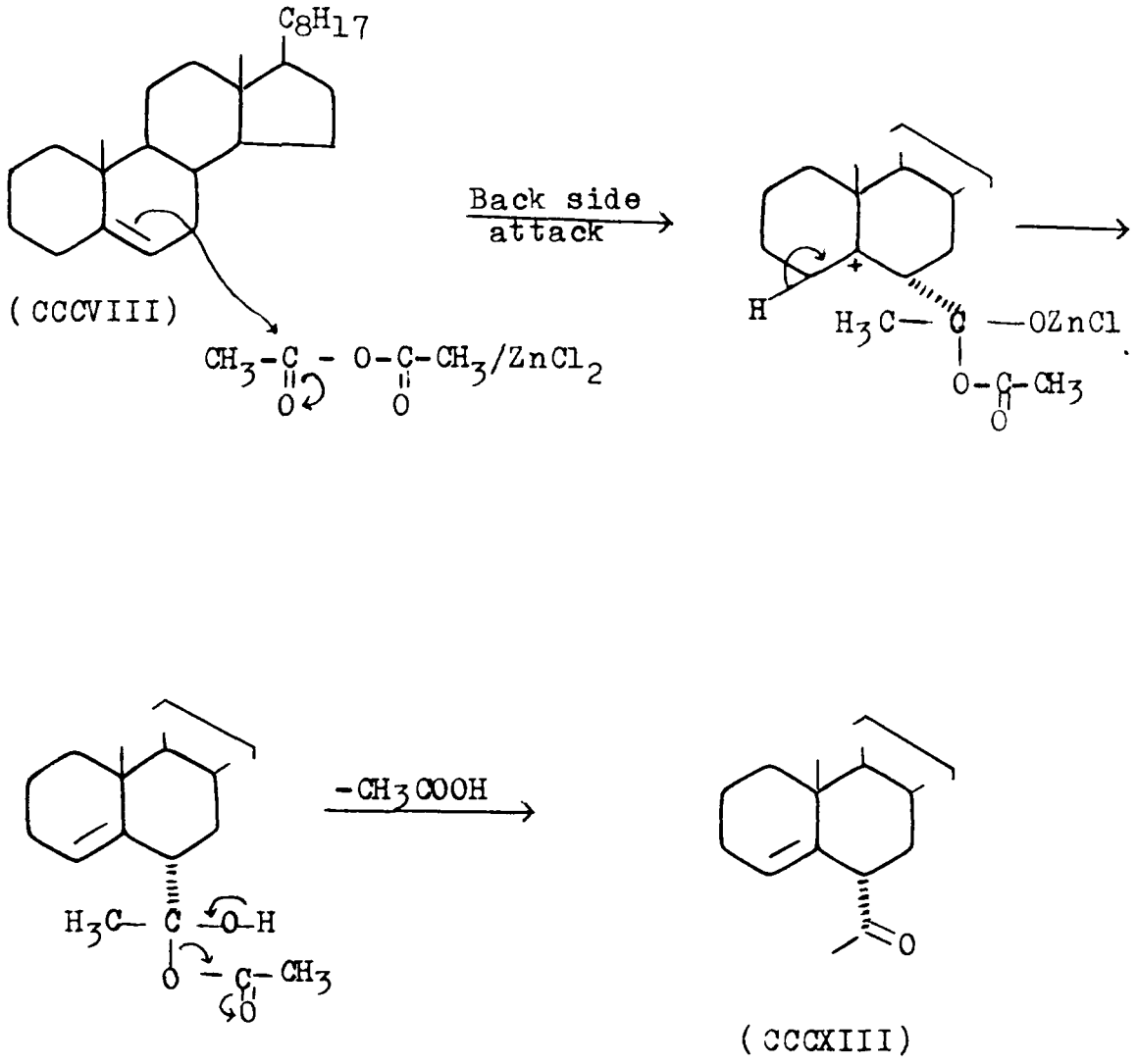
The NMR spectrum showed signals at δ 4.95 (1 proton), 3.1 (1 proton), 2.0 (3 protons), 1.03 (3 protons), 0.9, 0.8 and 0.65 (methyl protons).

The multiplet at δ 4.95 was attributed to the C_4-vinylic proton whereas the multiplet observed at δ 3.1 was ascribable to C_6-β proton (axial) rendering the acetyl group as equatorially oriented. This assignment is based on $W_{\frac{1}{2}}$ of the signal ($W_{\frac{1}{2}}$ 9 Hz) which is in agreement with axial proton[109]. Since the observation was compatible with the structure (CCCXIII), the alternate structure (CCCXII) could be discarded where C_6-α proton (equatorial) would have given a much sharper signal with $W_{\frac{1}{2}}$ of about 3-4 Hz. The signal for methyl protons of acetyl group was noted at δ 2.0 and the singlet seen at δ 1.03 was assigned to C_{10}-methyl protons.

On the basis of these spectral evaluations the compound m.p. 126° could be characterized as 6α-acetylcholest-4-ene (CCCXIII).

The mechanism of formation of the compound (CCCXIII) from (CCCVIII) can be shown according to the Scheme - III[104].

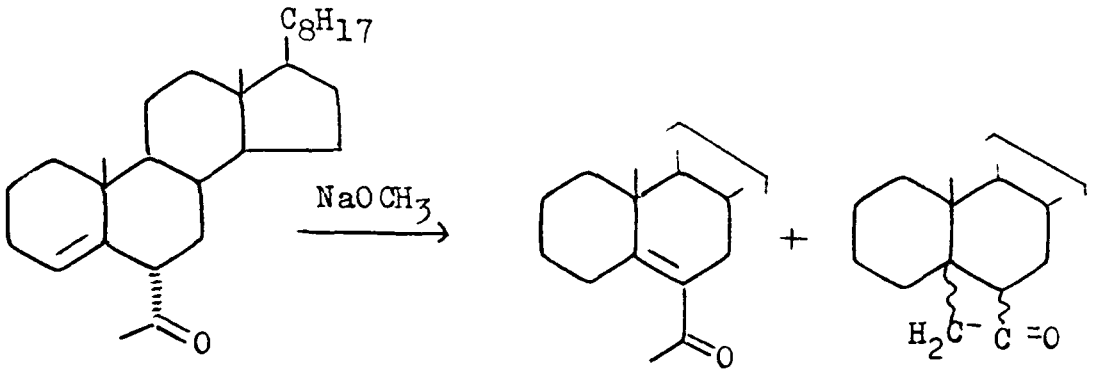
SCHEME - III



The characterization of the compound is further supported by its isomerization with sodium methoxide and oximation.

Reaction of 6α-Acetylcholest-4-ene (CCCXIII) with Sodium methoxide

6α-Acetylcholest-4-ene (CCCXIII) on heating under reflux with sodium methoxide provided an inseparable mixture of two isomeric compounds, 6-acetylcholest-5-ene (CCCXIV) and cholest-5-ene 5,6-ketene adduct (CCCXV) identified tentatively on the basis of spectral data obtained.



(CCCXIII) (CCCXIV) (CCCXV)

Characterization of the Oily Substance as an Inseparable Mixture of 6-Acetylcholest-5-ene (CCCXIV) and Cholest-5-ene 5,6-ketene adduct (CCCXV)

The oily product showed the presence of two compounds in the t.l.c. and it analysed for $C_{29}H_{48}O$. The IR spectrum exhibited absorption frequencies at 1770, 1685 and 1650 cm^{-1}. The band at 1770 was attributed to a four membered ring ketone

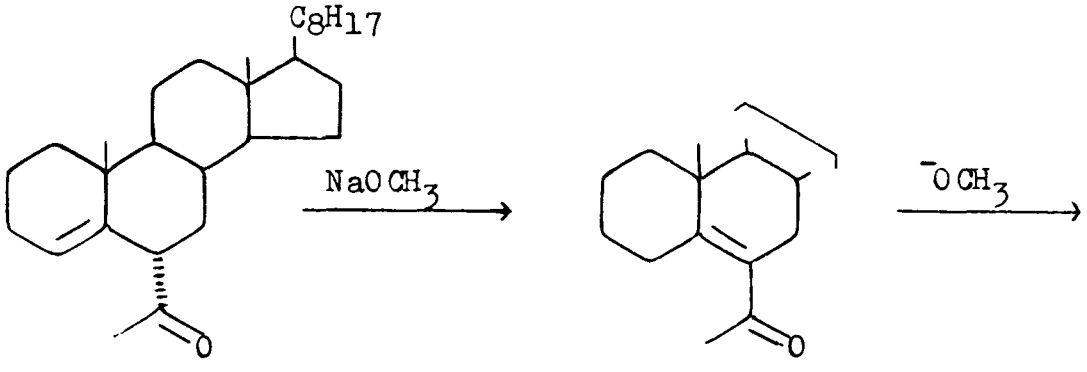
moiety[110] which can be accounted for by considering the structure (CCCXV). The α,β-unsaturated carbonyl chromophore was observed at 1685 and 1650 cm^{-1} (C=C-C=O) as in structure (CCCXIV). The molecular composition, t.l.c. and the IR spectral values suggested the presence of two isomeric compounds suchas (CCCXIV) and (CCCXV).

The NMR spectrum of the oil did not show any signal in the region for olefinic proton. A signal at δ 3.1 was due to C_6-$\underline{H}$ ($W_{\frac{1}{2}}$ 8 Hz) whereas the singlet at δ 2.05 was assigned for the methyl protons of the acetyl group as in the structure (CCCXIV). Remaining methyl signals were observed at δ 1.1, 0.9, 0.8 and 0.7.

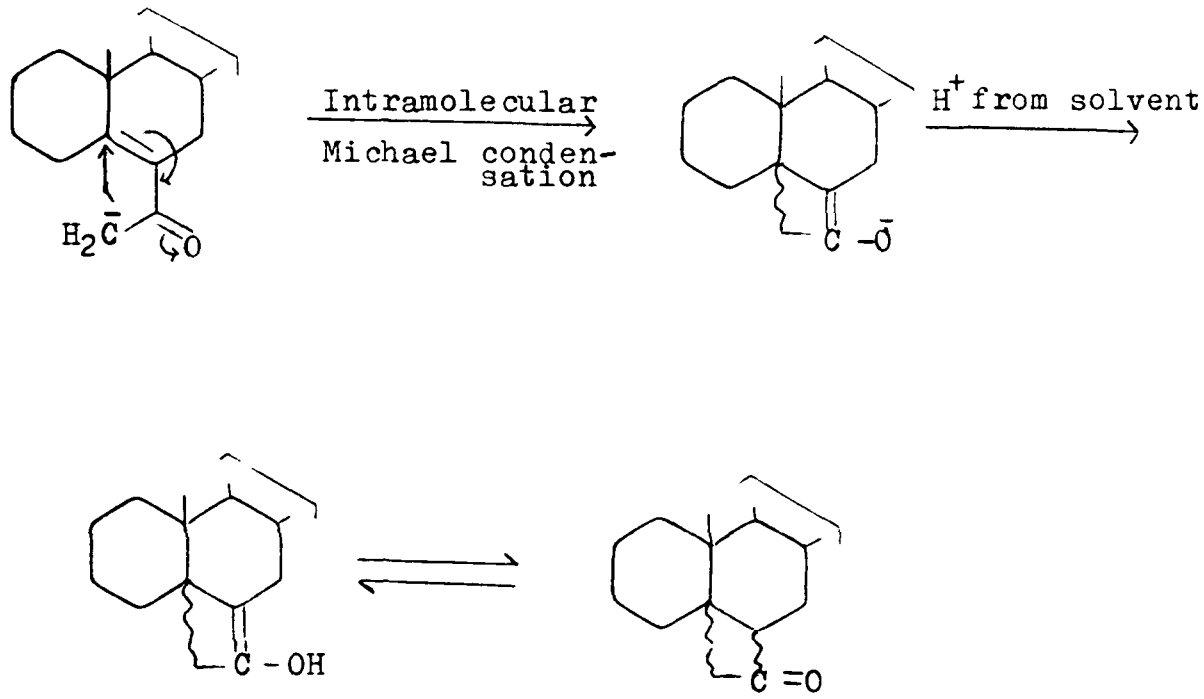
On the basis of the preceding discussion, the oil could best be suspected as an inseparable mixture of two isomers, suchas 6-acetylcholest-5-ene (CCCXIV) and (CCCXV)[tentatively named as cholest-5-ene 5,6-ketene adduct].

The formation of (CCCXV) may be shown according to the Scheme - IV.

SCHEME - IV



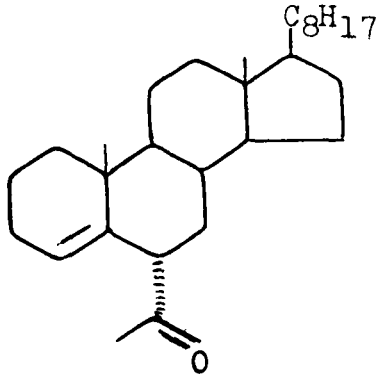
(CCCXIII) (CCCXIV)



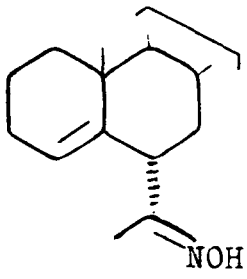
(CCCXV)

Reaction of 6α-Acetylcholest-4-ene (CCCXIII) with Hydroxylamine hydrochloride and Sodium acetate trihydrate : 6α-Acetylcholest-4-en-1'-oxime (CCCXVI)

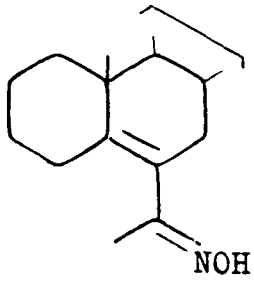
6α-Acetylcholest-4-ene (CCCXIII) on treatment with hydroxylamine hydrochloride and sodium acetate trihydrate afforded an oily compound analysed for $C_{29}H_{49}NO$.



(CCCXIII)



(CCCXVI)



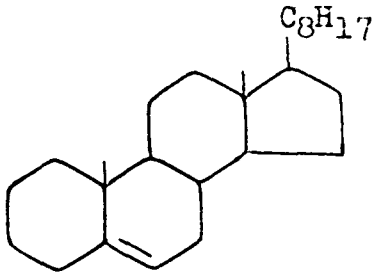
(CCCXVII)

The IR spectrum of the compound gave bands at 3280, 1640 and 1620 cm^{-1} assigned for -OH, C=N and C=C frequencies, respectively. The elemental analysis and IR spectral data may also hold good for its alternate structure (CCCXVII). However, (CCCXVI) was preferred over (CCCXVII) on the basis of its NMR spectrum which exhibited a multiplet integrating for one proton at δ 5.0 assigned to C_4-vinylic proton. Further support to this structure was due to the appearance of a one proton multiplet of C_6-β$\underline{H}$ (axial) at δ 3.0 ($W_{\frac{1}{2}}$ 8 Hz). A three proton singlet was noted at δ 1.8 ($C\underline{H}_3$-C=NOH). Remaining methyl signals were obtained at δ 1.43, 1.33, 1.26, 0.95 and 0.83.

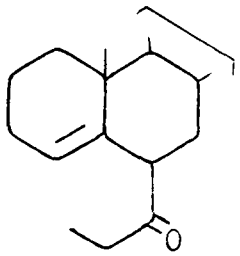
Thus on the basis of the above evidences the oil was characterized as 6α-acetylcholest-4-en-1'-oxime (CCCXVI).

Reaction of cholest-5-ene (CCCVIII) with Propionic anhydride and Zinc chloride : 6β-Propanylcholest-4-ene (CCCXVIII)

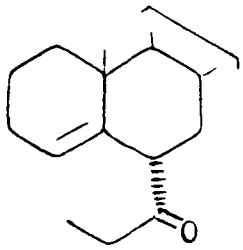
Cholest-5-ene (CCCVIII) on similar pattern of acylation using propionic anhydride and dry zinc chloride furnished a compound, m.p. 99° analysed for $C_{30}H_{50}O$.



(CCCVIII)



(CCCXVIII)



(CCCXIX)

The IR spectrum of the compound showed strong band at 1710 and a medium band at 1650 cm^{-1} for exocyclic saturated carbonylchromophore and olefinic linkage, respectively. Thus the presence of a propanyl function was evident from the elemental analysis and IR spectral data. Therefore, two isomeric structures (CCCXVIII) and (CCCXIX) could be formulated for the compound and the conclusive distinction between the two isomers was done on the basis of its NMR spectrum.

The NMR signals were observed at δ 5.65 (1 proton), 2.8 (1 proton), 2.4 (2 protons), 1.8, 1.63, 1.2, 1.08, 0.85 and 0.7 (methyl protons).

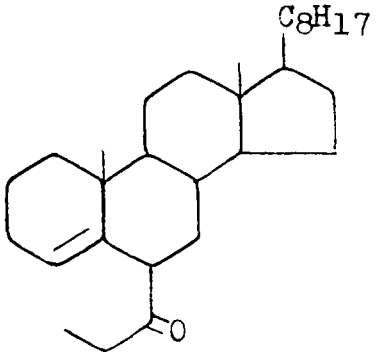
The multiplet at δ 5.65 was attributed to the C_4-vinylic proton whereas the multiplet observed at δ 2.8 ($W\frac{1}{2}$ 3 Hz) was due to the C_6-α proton (equatorial) rendering the propanyl group as axially oriented. Since the observation was compatible with the structure (CCCXVIII) the possibility of the alternate structure (CCCXIX) was ruled out. The signal for α-methylene proton of propanyl group (as quartet) was seen at δ 2.4 (J = 7.5 Hz).

On the basis of the above discussion, the compound, m.p. 99° can best be characterized as 6β-propanylcholest-4-ene (CCCXVIII).

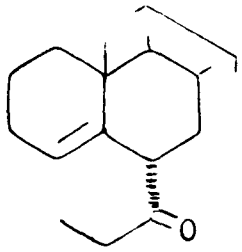
The formation of the compound, m.p. 99° as (CCCXVIII) is further supported on the basis of its isomerization and oximation.

Isomerization of 6β-Propnaylcholest-4-ene (CCCXVIII) with Sodium methoxide : 6α-Propanylcholest-4-ene (CCCXIX)

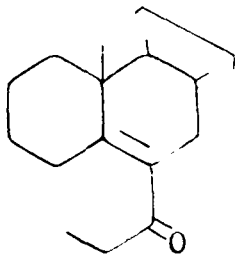
The ketone (CCCXVIII) on treatment with sodium methoxide afforded a crystalline product, m.p. 112° analysed for $C_{30}H_{50}O$.



(CCCXVIII)



(CCCXIX)



(CCCXX)

The IR spectrum of the compound gave absorption bands at 1710 cm^{-1} for carbonyl function of propanyl group whereas the band at 1650 cm^{-1} was due to C=C stretching. Since the IR values were in accordance with the structure (CCCXIX) only, the possibility of the alternate structure (CCCXX) was ruled out because it required the appearance of the band for carbonyl chromophore (C=C-C=O) at 1680-1690 cm^{-1}. Further support to the structure had come from its NMR spectrum which showed signals at δ 4.88(1 proton), 3.13 (1 proton), 2.4 (2 protons), 1.8, 1.63, 1.2, 1.08, 0.85 and 0.7 (methyl protons).

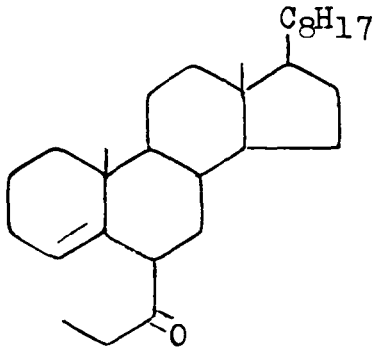
The multiplet for one proton at δ 4.88 was due to the C_4-vinylic proton and the multiplet at δ 3.13 ($W_{\frac{1}{2}}$ 9 Hz) integrating for one proton was attributed to the C_6-β proton (axial) rendering the propanyl group as equatorially oriented. The change in the orientation of propanyl group from axial

(CCCXVIII) to equatorial (CCCXIX) was indirectly suggested by the upfield shift of C_4-vinylic proton from δ 5.65 to 4.88 during isomerization as discussed earlier. A quartet for two protons noted at δ 2.4 (J = 7 Hz) was ascribable to α-methylene protons of propanyl group.

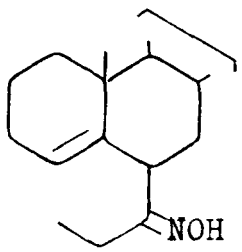
Thus on the basis of preceding discussion the compound m.p. 112° could be characterized as 6α-propanylcholest-4-ene (CCCXIX).

Reaction of 6β-Propanylcholest-4-ene (CCCXVIII) with Hydroxyl amine hydrochloride and Sodium acetate trihydrate : 6-Propanyl--cholest-5-en-1'-oxime (CCCXXII)

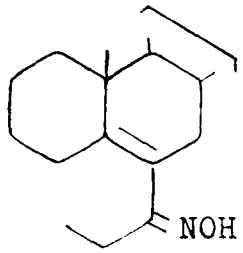
The ketone (CCCXVIII) on treatment with hydroxyl amine hydrochloride and sodium acetate trihydrate afforded a compound, m.p. 187° which, analysed for $C_{30}H_{51}NO$.



(CCCXVIII)



(CCCXXI)



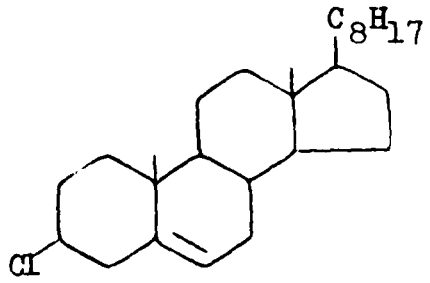
(CCCXXII)

The IR spectrum showed absorption bands at 3280 and 1660 cm^{-1}. The band at 3280 can be assigned to the hydroxy grouping of oxime function whereas the band noted at 1660 cm^{-1} was due to C=N and C=C stretchings. The molecular composition and IR values were in full agreement with both the isomeric structures (CCCXXI) and (CCCXXII). However, the conclusive distinction between the two was made on the basis of its NMR spectral data.

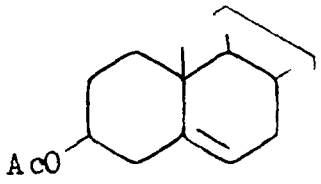
The NMR spectrum of the compound did not show any signal in the region for olefinic protons which eliminated the possibility of the structure (CCCXXI). The C=N-O<u>H</u> signal was also not seen upto δ 8.0. However, IR spectrum does support the presence of an oximino group without any doubt. Thus on the basis of the above mentioned observations the compound, m.p. 187° can be characterized as 6-propanylcholest-5-en-1'-oxime (CCCXXII).

<u>Reaction of 3β-Chlorocholest-5-ene (CCCIX) with Acetic anhydride and Zinc chloride : 3β-Acetoxycholest-5-ene (CCCX)</u>

3β-Chlorocholest-5-ene (CCCIX) on similar treatment of acylation using acetic anhydride and dry zinc chloride gave only one product m.p. 115° which was characterized as 3β-acetoxy--cholest-5-ene (CCCX) on the basis of m.p., m.m.p. and spectral values[111].



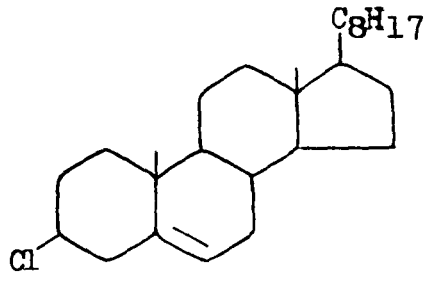
(CCCIX)



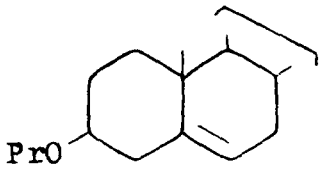
(CCCX)

Reaction of 3β-Chlorocholest-5-ene (CCCIX) with Propionic anhydride and Zinc chloride : 3β-Propionoxycholest-5-ene (CCCXXIII)

3β-Chlorocholest-5-ene (CCCIX) with propionic anhydride and dry zinc chloride under usual conditions of the reaction gave a single compound, m.p. 100°, identified as 3β-propionoxycholest-5-ene (CCCXXIII) on the basis of m.p., m.m.p. and spectral values[112].



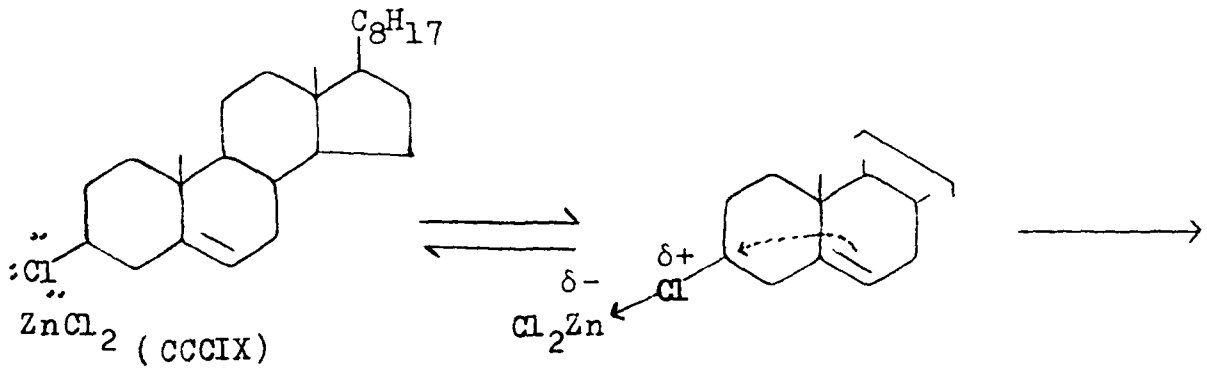
(CCCIX)

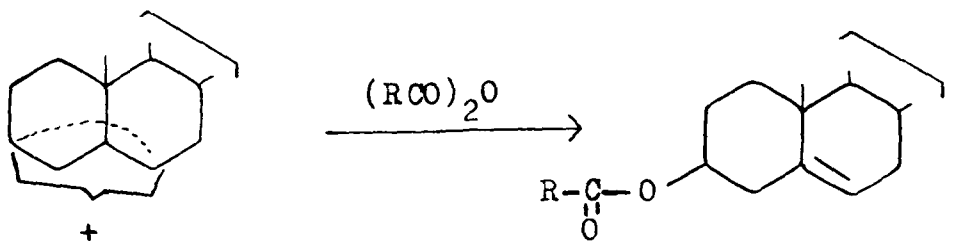


(CCCXXIII)

In these two cases, the 3β-chlorine was substituted by RCOO-group and no reaction did occur at the double bond. The formation of esters (CCCX) and (CCCXXIII) can be accounted for by the following process (Scheme - V) which involves neighbouring group participation by C_5-C_6 double bond.

SCHEME - V





(CCCX) R, CH_3

(CCCXXIII) R, C_2H_5

It appears that the zinc chloride complexes with the halogen in steroid leading to the above reaction thus rendering C_5-C_6 double bond unavailable for the Friedel-Crafts' like reaction.

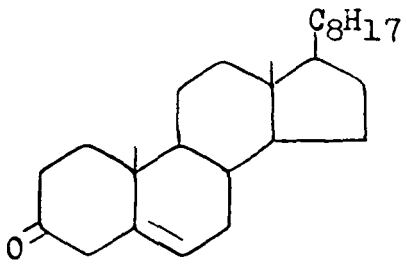
Reaction of 3β-Acetoxycholest-5-ene (CCCX) with Anhydrides and Zinc chloride

3β-Acetoxycholest-5-ene (CCCX) failed to react with acetic anhydride or propionic anhydride in presence of dry zinc chloride under the condition mentioned earlier. In both the cases the unreacted olefin was isolated in about 95% yield.

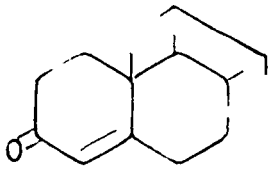
It is important to note that the desired β,γ-unsaturated ketones were not obtained from the Δ^5-olefins in presence of substituent at C_3, under our reaction conditions.

Reaction of Cholest-5-en-3-one (CCCXI) with Acetic anhydride and Zinc chloride

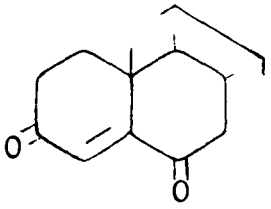
The ketone (CCCXI) under similar conditions of acylation using acetic anhydride and dry zinc chloride followed by the usual work up and column chromatography over silica gel furnished three products, m.p. 80°, 123° and 100°.



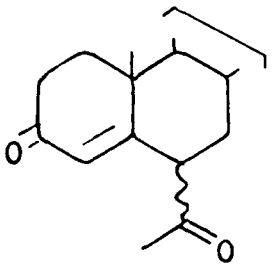
(CCCXI)



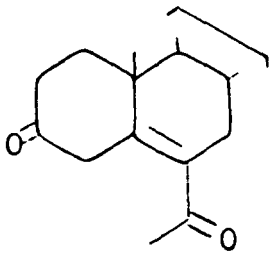
(LXXVIII)



(CXII)



(CCCXXIV)



(CCCXXV)

Identification of the compound m.p. 80° as cholest-4-en-3-one (LXXVIII)

The compound m.p. 80° was found to be identical in all respects (t.l.c., m.p., m.m.p., IR and NMR) with an authentic sample of cholest-4-en-3-one (LXXVIII)[113].

Identification of the compound m.p. 123° as cholest-4-ene-3,6-dione (CXII)

The compound m.p. 123° has been characterized as cholest-4 -ene-3,6-dione (CXII)on the basis of t.l.c., m.p., m.m.p. and spectral values (IR and NMR)[114].

Characterization of the compound m.p. 100° as 6β-acetylcholest-4-en-3-one (CCCXXIV)

The compound m.p. 100° analysed for $C_{29}H_{46}O_2$. This showed the incorporation of an acetyl group (CH_3CO) in the starting ketone (CCCXI). The IR spectrum of the compound exhibited absorption bands at 1710, 1680 and 1615 cm^{-1}. The sharp bands at 1710 and 1680 cm^{-1} could be attributed to the isolated carbonyl chromophore (C=O) and α,β-unsaturated carbonyl function (C= C-C=O), respectively. In addition to these a medium band at 1615 cm^{-1} was assigned to the C=C stretching frequency.

The molecular composition and IR spectral values were in good agreement with both the probable structures (CCCXXIV) and (CCCXXV) for the compound and not sufficient to make distinction between the two. However, the assignment of the correct structure to the compound was aided by its NMR spectrum which gave signals at δ 5.96 s(1H, C_4-H), 3.2 m(1H, C_6β-H, $W_{\frac{1}{2}}$ 9 Hz), 2.13 s(3H, CH_3CO), 1.25 s(C_{10}-CH_3), 1.0, 0.9, 0.8 and 0.7 (methyls).

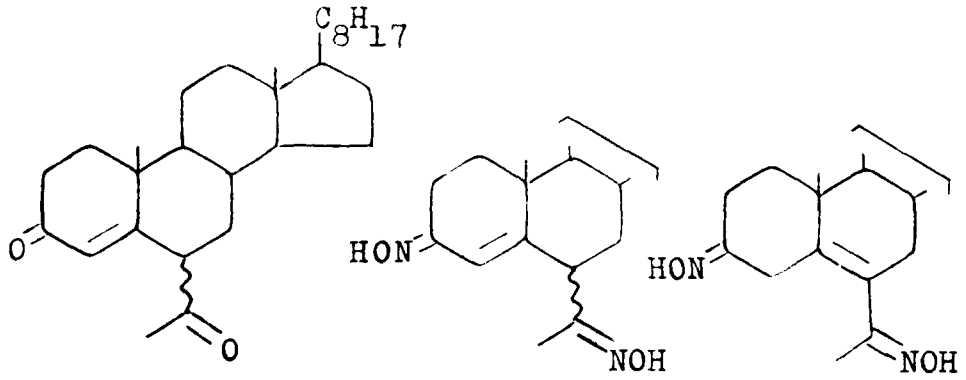
The important signal at δ 5.96 as a singlet for one proton was due to the C_4-vinylic proton and hence discarded the possibility of the structure (CCCXXV) where vinylic proton is absent.

The assignment of the structure (CCCXXIV) for the compound with uncertain configuration of the group at C_6 is based on two facts, the signal for C_6 proton at δ 3.2 with $W_{\frac{1}{2}}$ 9 Hz is in favour of the proton being axially oriented whereas the signal for C_4-vinylic proton at δ 5.96 [which is at lower field as compared to the C_4-vinylic proton of an authentic sample of cholest-4-en-3-one (LXXVIII)[113] at δ 5.66] is in favour of the axial orientation of the C_6 acetyl group as discussed earlier.

Further investigation may enable to ascertain the configuration and provide reasons for the chemical shifts observed. At present the compound m.p. 100°, has been characterized as 6ϱ-acetylcholest-4-en-3-one (CCCXXIV).

Oximation of 6ϱ-Acetylcholest-4-en-3-one (CCCXXIV) : 6-Acetylcholest-5-en-3-one-1',3-dioxime (CCCXXVII)

The ketone (CCCXXIV) on treatment with hydroxylamine hydrochloride and sodium acetate trihydrate followed by the usual workup and column chromatography over silica gel furnished a compound m.p. 145° analysed for $C_{29}H_{48}N_2O_2$.



(CCCXXIV) (CCCXXVI) (CCCXXVII)

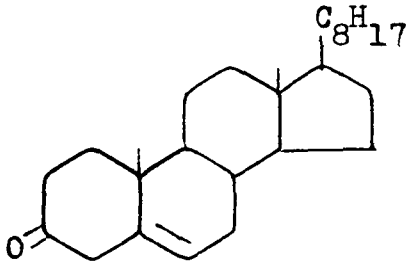
The IR spectrum of the compound with bands at 3240, 1650 and 1630 cm^{-1} suggested the presence of -OH, C=N and C=C moieties, respectively. It was evident from the elemental analysis and IR values that both the keto groups have undergone oximation. The establishment of the correct structure was done on the basis of its NMR spectrum since IR data may hold good for both the probable structures (CCCXXVI) and (CCCXXVII).

The NMR spectrum exhibited signal at δ 7.0 integrating for 2 protons was assigned to hydroxy protons of oxime functions whereas a three protonsbroad singlet noted at δ 2.1 was ascribable to CH_3-C=NOH. Absence of any other downfield signal for any vinylic proton ruled out the possibility of the structure (CCCXXVI). Other methyl signals were observed at δ 1.2, 0.91, 0.8 and 0.6.

On the basis of the above discussions the compound m.p. 145° was characterized as 6-acetylcholest-5-en-3-one-1',3-dioxime (CCCXXVII).

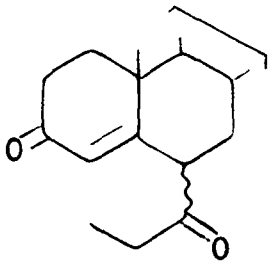
Reaction of Cholest-5-en-3-one (CCCXI) with Propionic anhydride and Zinc chloride

Cholest-5-en-3-one (CCCXI) when subjected to Friedel-Crafts' acylation, in the manner as discussed earlier using propionic anhydride and dry zinc chloride afforded two compounds, m.p. 80° and 119°.

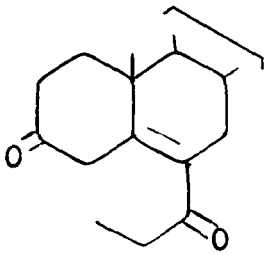


(LXXVIII)

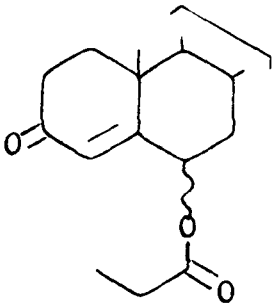
(CCCXI)



(CCCXXVIII)



(CCCXXIX)



(CCCXXX)

Identification of the compound m.p. 80° as cholest-4-en-3-one (LXXVIII)

The compound m.p. 80° has been identified as cholest-4-en-3-one (LXXVIII) on the basis of t.l.c., m.p., m.m.p. and spectral values (IR and NMR)[113].

Characterization of the compound m.p. 119° as 6ξ-propionoxy-cholest-4-en-3-one (CCCXXX)

The compound m.p. 119° analysed for $C_{30}H_{48}O_3$. The composition suggested the addition of $C_3H_4O_2$ moiety to the substrate (CCCXI) during the reaction. This can be accounted for by considering the substitution of a propionoxy group at C_6 to give the product, m.p. 119°. The IR spectrum of the compound exhibited absorption bands at 1740 and 1680 cm^{-1} which could be attributed to the propionoxy carbonyl chromophore ($O-\overset{O}{\overset{\|}{C}}-C_2H_5$) and α,β-unsaturated carbonyl function, respectively.

The molecular composition and IR spectral values were in good agreement with the probable structure (CCCXXX) only and hence discarded other possibilities suchas (CCCXXVIII) and (CCCXXIX).

Further support to the structure (CCCXXX) has come from its NMR spectrum which gave signals at δ 5.7s (1H, $C_4-\underline{H}$), 5.45m (1H, $C_6\xi-\underline{H}$, $W_{\frac{1}{2}}$ 9 Hz), 2.36br,m (4H, $C_2-\underline{H}_2$ and $CH_3-C\underline{H}_2-COO-$),

1.18, 1.1, 0.9, 0.8 and 0.7 (methyl groups).

The sharp singlet at δ 5.7 for 1 proton was attributed to the C_4-vinylic proton and the multiplet at δ 5.45 with $W_{\frac{1}{2}}$ 9 Hz was ascribed to the proton attached to C_6, bearing the propionoxy group.

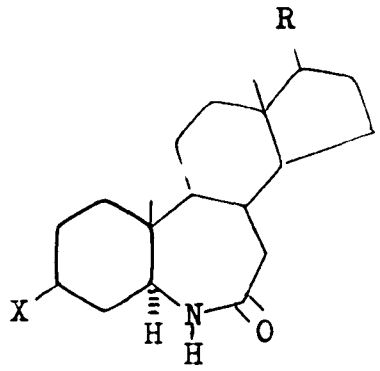
The compound m.p. 119° is formulated as 6ξ-propionoxy-cholest-4-en-3-one (CCCXXX) with uncertain configuration on the basis of the reasons advanced in the earlier discussion.

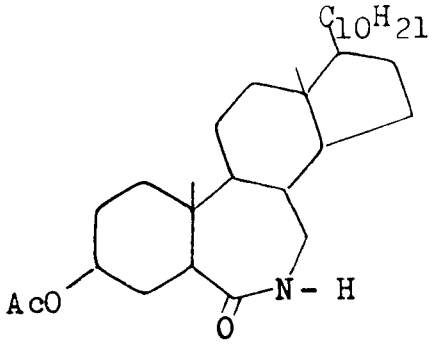
PART - I(B)

AZASTEROIDS

The Beckmann rearrangement and the Schmidt reaction of steroidal ketoximes and ketones, respectively, are the two frequently employed methods for the insertion of nitrogen atom into the steroidal framework.

Previous work from our laboratory has described the Beckmann rearrangement and the Schmidt reaction of several steroidal ketoximes and ketones in order to prepare azasteroids of probable biological potential. The work was mainly concerned with the cholestane and the stigmastane series and as a consequence a large number of the then unknown azasteroids were synthesized. These azasteroids are (XXXI, LVIII)[20], (XXXII, XXXVII)[21], (XXXIII, XCVII)[22], (LV, LVII)[32], (CVIII, CIX, CX)[48], (CXIII, CXIV)[50], (CXX)[52], (CXXXIII, CXXXIV, CXXXV, CXXXVII, CXXXIX, CXL and CXLIII)[55].





(CXXXIII)

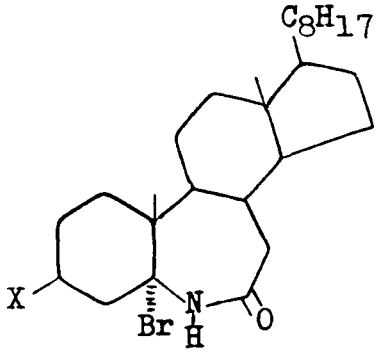
(XXXI) X, Cl; R, C_8H_{17}

(XXXII) X, Br; R, C_8H_{17}

(XXXIII) X, I ; R, C_8H_{17}

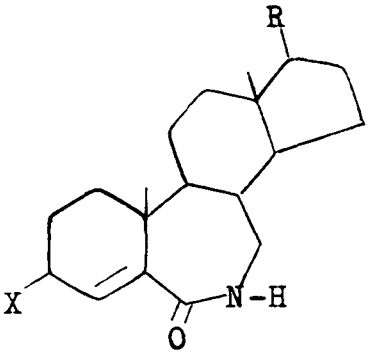
(CXXXIV) X, Cl; R, $C_{10}H_{21}$

(CXXXV) X, OH; R, $C_{10}H_{21}$



(LV) X, OH

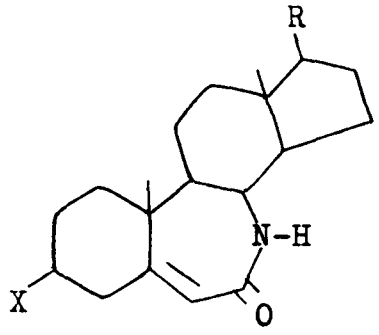
(LVII) X, H

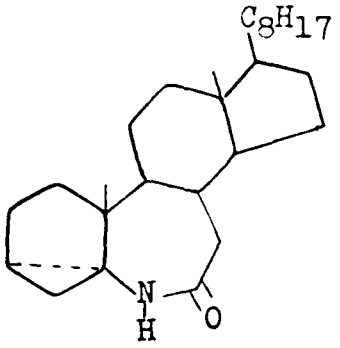


(LVIII) X, H; R, C_8H_{17}

(XCVIII) X, OAc; R, C_8H_{17}

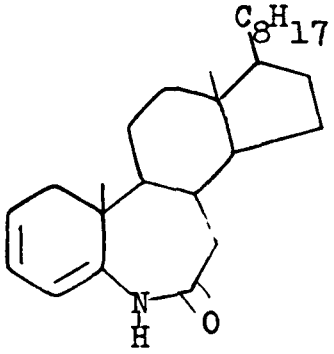
(CXXXVII) X, OAc; R, $C_{10}H_{21}$



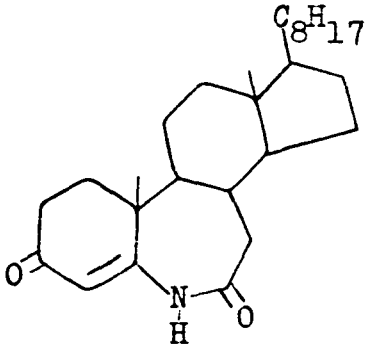


(CIX)	X, H;	R,	C_8H_{17}
(CX)	X, OH;	R,	C_8H_{17}
(CVIII)	X, OAc;	R,	C_8H_{17}
(CXLIII)	X, H;	R,	$C_{10}H_{21}$
(CXXXIX)	X, OAc;	R,	$C_{10}H_{21}$

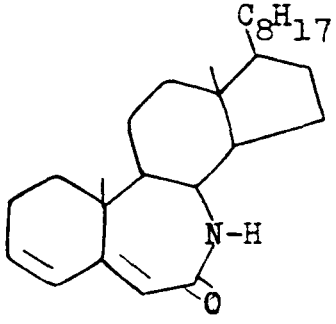
(XXXVII)



(CXIII)

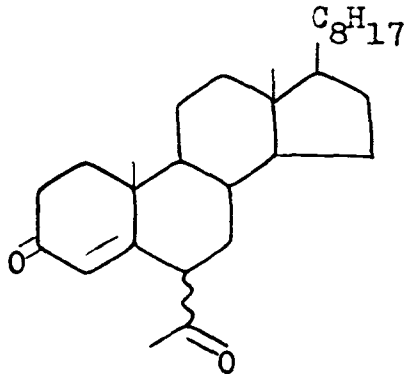


(CXIV)

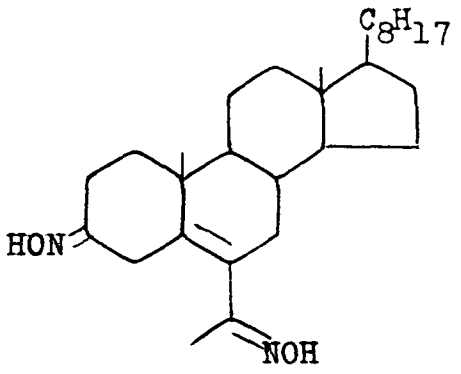


(CXX)

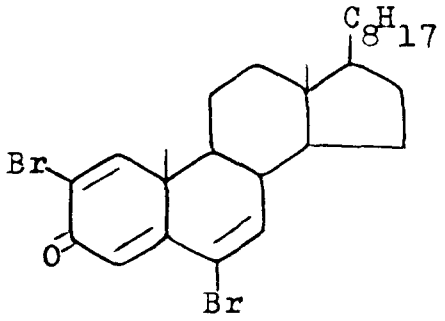
As an extension of the above work, some of the easily accessible steroidal ketones and ketoximes suchas, 6ϱ-acetylcholest-4-en-3-one (CCCXXIV), 2,6-dibromocholesta-1,4,6-trien-3-one (CCCXXXVI) and 6-acetylcholest-5-en-3-one-1',3-dioxime (CCCXXVII) were subjected to the Schmidt reaction and the Beckmann rearrangement in order to prepare hitherto unsynthesized azasteroids. The characterization of the products thus obtained was done on the basis of their elemental analysis and spectral properties.



(CCCXXIV)



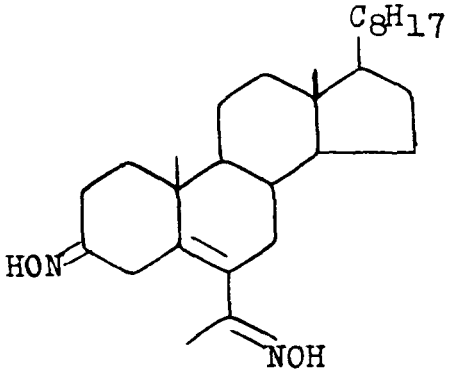
(CCCXXVII)



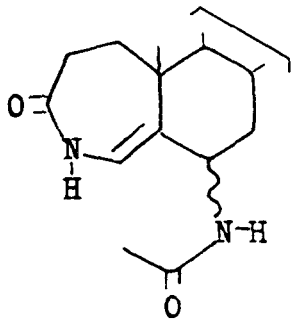
(CCCXXXVI)

Beckmann rearrangement of 6-Acetylcholest-5-en-3-one-1',3-dioxime (CCCXXVII)

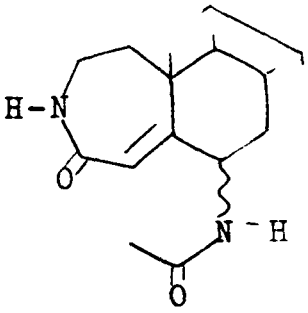
The oxime (CCCXXVII), subjected to the Beckmann rearrangement (using thionylchloride at 0°C followed by treatment with 4N potassium hydroxide solution), afforded two compounds m.p. 240° and an oil 'A'.



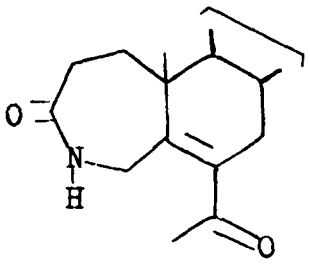
(CCCXXVII)



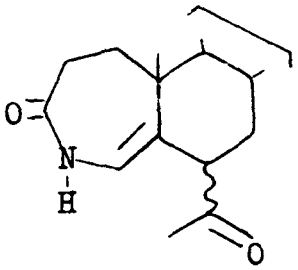
(CCCXXXI)



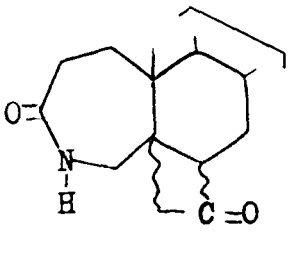
(CCCXXXII)



(CCCXXXIII)



(CCCXXXIV)



(CCCXXXV)

Characterization of the compound m.p. 240° as 6ξ-N-acetamido-4-aza-A-homocholest-4a-en-3-one (CCCXXXI)

The compound m.p. 240° analysed for $C_{29}H_{48}N_2O_2$. The IR spectrum exhibited absorption bands at 3360, 1660 and 1610 cm^{-1}. The band at 3360 can be assigned to N-H stretching whereas the band at 1660 cm^{-1} was due to NH-C=O. Another band at 1610 cm^{-1} was ascribable to C=C frequency. The molecular composition and IR spectral data suggested two isomeric structures (CCCXXXI) and (CCCXXXII) for the compound m.p. 240°. So in order to arrive at a reasonable conclusion regarding the structure, its NMR spectrum was examined.

The NMR spectrum of the compound showed a broad signal at δ 6.4 integrating for two protons (exchangeable with deuterium) and was assigned to the two N-H protons. Another signal as broad singlet (simplified on D_2O shake) for one proton noted at δ 5.83 was ascribable to C_{4a}-vinylic proton. This particular signal provided an idea about the migration of double bond from C_5-C_6 to C_4-C_5 during the course of the reaction which was further supported by the appearance of one proton multiplet for C_6-ξH at δ 3.2 ($W_{\frac{1}{2}}$ 9 Hz). Since these two significant signals hold good for both the isomeric structures (CCCXXXI) and (CCCXXXII) so the conclusive distinction between the two was made possible with the help of

C_2 methylene proton signal, which was observed at δ 2.4 as multiplet and suggested the structure (CCCXXXI) for the compound because the alternate structure (CCCXXXII) required its apperance at lower field due to neighbouring nitrogen present as a part of the ring[29]. In addition to these a three proton singlet seen at δ 2.0 was due to $CH_3\overset{O}{\overset{\|}{C}}-NH-$. Remaining methyl signals were obtained at δ 1.05, 0.85, 0.78 and 0.6. On the basis of the above spectral evidences the compound m.p. 240° was characterized as 6ξ-N-acetamido-4-aza-A-homocholest-4a-en-3-one (CCCXXXI).

Characterization of the oil 'A' as 4-aza-A-homocholest-5-en-3-one 5,6-ketene adduct (CCCXXXV)

The oil 'A' analysed for $C_{29}H_{47}NO_2$. The molecular composition suggested three possible isomeric structures (CCCXXXIII), (CCCXXXIV) and (CCCXXXV) for the compound,

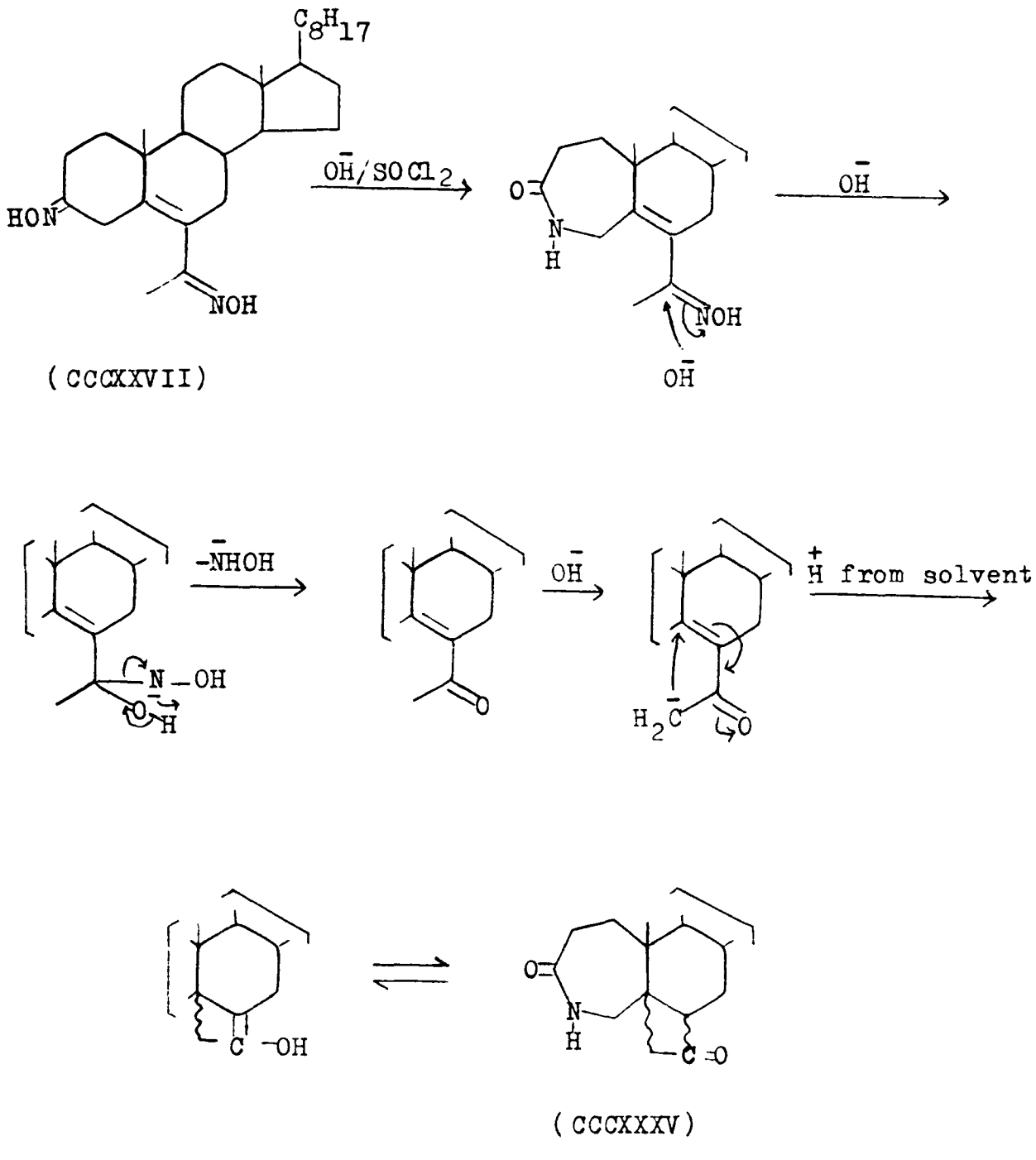
The IR spectrum showed absorption bands at 3200, 1770 and 1660 cm^{-1}. The band at 3200 was assigned to NH stretching whereas the band at 1770 cm^{-1} was ascribable to an additional four membered ring ketone moiety[109] as in the structure (CCCXXXV). Another band at 1660 cm^{-1} was due to -CONH function.

Since the IR spectrum was devoid of the bands at 1610, 1680-1690 and 1705 cm^{-1} the possibility of the isomeric

structures (CCCXXXIII) and (CCCXXXIV) was ruled out in favour of the isomer (CCCXXXV). This observation was further supported by its NMR spectrum which exhibited a signal at δ 6.5 integrating for one proton and was assigned to amido proton. The signal disappeared on D_2O shake. A multiplet for two protons at δ 4.2 was ascribed to C_{4a}-methylene protons which was further simplified on D_2O shake whereas another one protons multiplet at δ 3.13 ($W_{\frac{1}{2}}$ 8 Hz) was due to C_6-$\underline{H}$. Another signal as multiplet for two proton at δ 2.4 was ascribed to C_2-methylene protons. The NMR spectrum was devoid of any signal for methyl protons of acetyl group as required for the structures (CCCXXXIII) and (CCCXXXIV), provided further support to the cyclic structure (CCCXXXV).

Remaining methyl signals were observed at δ 1.26, 0.86, 0.8 and 0.56. Therefore, on the basis of the spectral values the oily product 'A' can provisionally be characterized as (CCCXXXV). The formation of (CCCXXXV) can be accounted for if we consider the normal Beckmann rearrangement and the deoximation of acetyl oximino group followed by the cyclization involving methyl carbon of acetyl group and C_5 as shown in Scheme - VI.

SCHEME - VI

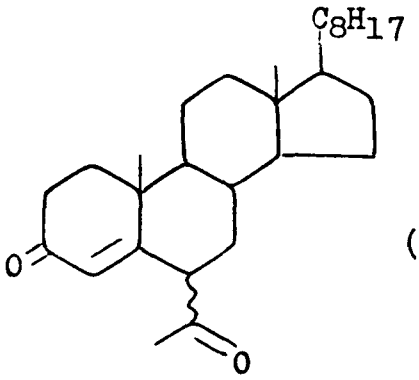


(CCCXXVII)

(CCCXXXV)

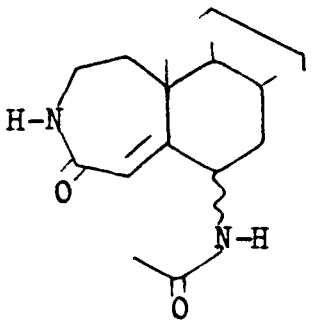
Schmidt reaction of 6ξ-Acetylcholest-4-en-3-one (CCCXXIV) : 6ξ-N-Acetamido-3-aza-A-homocholest-4a-en-4-one (CCCXXXII)

The Schmidt reaction of 6ξ-acetylcholest-4-en-3-one (CCCXXIV) after usual workup provided a single compound m.p. 172° analysed for $C_{29}H_{48}N_2O_2$.



(CCCXXIV)

(CCCXXXI)



(CCCXXXII)

IR spectrum showed absorption bands at 3300,1670, 1640 and 1610 cm^{-1}. The band at 3300 was assigned to NH stretching whereas the band at 1670 and 1640 cm^{-1} were attributed to CONH functions. Another band at 1610 cm^{-1} was ascribable to C=C frequency. The elemental composition and IR spectrum of the compound suggested that both acetyl and cyclic ketone have been affected during the reaction and the resultant nitrogenous compound has one of the two isomeric structures (CCCXXXI) and (CCCXXXII). The conclusive distinction between the two isomers was made on the basis of its NMR spectral data.

The NMR spectrum of the compound exhibited a broad signal at δ 7.0 integrating for two protons which was ascribable to two N-H protons. The signal disappeared after D_2O shake. One proton singlet at δ 5.8 was attributed to C_4-vinylic proton. Another broad multiplet (simplified on D_2O shake) for two protons at δ 4.5 was ascribed to the C_2-methylene protons. Therefore, the possibility of the structure (CCCXXXI) was ruled out because in that case the C_2-methylene protons would have appeared at comparatively higher field. At δ 3.2 ($W_{\frac{1}{2}}$ 9 Hz) a multiplet for one proton was observed, which was assigned to the C_6-$\underline{6}H$. In addition to these, a three protons singlet for methyl protons of $\underline{CH}_3$-CONH function was observed at δ 2.0. Other methyl signals were observed at δ 1.08, 0.9, 0.8 and 0.7.

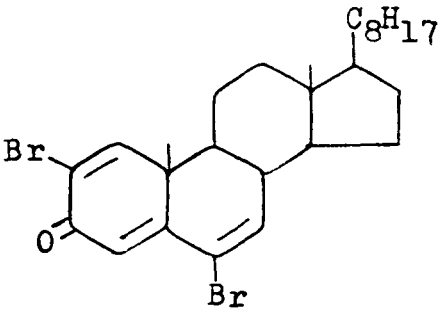
On the basis of the above spectral properties the compound m.p. 172° has been characterized as 6ξ-N-acetamido-3-aza-A-homocholest-4a-en-4-one (CCCXXXII).

Schmidt reaction of 2,6-Dibromocholesta-1,4,6-trien-3-one (CCCXXXVI)

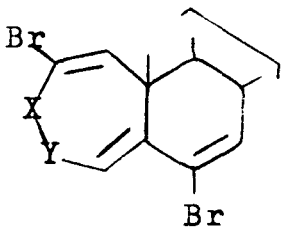
The dibromo ketone (CCCXXXVI) was prepared according to the literature procedure[115]. [ν_{max} 1660s (C=C-$\overset{O}{\overset{\|}{C}}$-C=C), 1610 (C=C) and 760 cm^{-1} w(C-Br); δ 7.23s (1H, C_1-vinylic proton), 6.46s (1H, C_4-vinylic proton), 6.3d (1H, C_7-vinylic

proton), 1.28s (3H, C_{10}-methyl protons),0.9, 0.8 and 0.73 (other methyl groups)]. The spectral data for the ketone (CCCXXXVI) were obtained for total identification and comparison purpose.

The Schmidt reaction of 2,6-dibromocholesta-1,4,6-trien-3-one (CCCXXXVI) after usual workup and column chromatography over silica gel furnished two products, non-crystallizable oil 'S_1' and a crystalline product m.p. 220°.

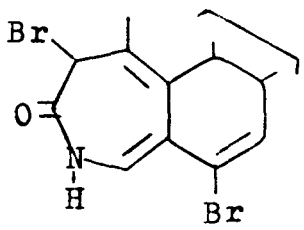


(CCCXXXVI)

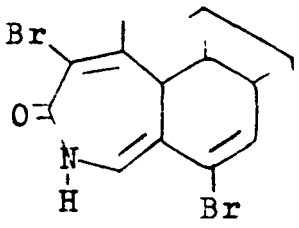


(CCCXXXVII) X, NH; Y, CO

(CCCXXXVIII) X, CO; Y, NH



(CCCXXXIX)



(CCCXL)

Characterization of the oil 'S_1' as 4-aza-A-homo-19-nor-1-methyl-2,6-dibromocholesta-1(10),4a,6-trien-3-one (CCCXXXIX)

The oil 'S_1' gave positive Beilstein test and analysed for $C_{27}H_{39}NOBr_2$. The IR spectrum exhibited absorption bands at 3500, 3200, 1670, 1610 and 760 cm^{-1}. The bands at 3500, 3200 were due to NH stretching whereas the band at 1670 cm^{-1} was assigned to $-\overset{O}{\overset{\|}{C}}-NH$ function. Another band at 1610 cm^{-1} was ascribed to C=C stretching frequency. In addition to these, a significant band for C-Br linkage was noted at 760 cm^{-1}. The molecular composition, halogen test and IR spectral data suggested four isomeric structures (CCCXXXVII-CCCXL) for the compound. So in order to arrive at a reasonable conclusion regarding the structure, its NMR spectrum was examined. It gave a broad multiplet for two protons at δ 6.5 ascribable to C_{4a}- and C_7-vinylic protons. A singlet observed at δ 4.3 integrating for one proton was attributed to C_2- H compatible with the structure (CCCXXXIX) only. Hence this observation ruled out the possibility of the structures (CCCXXXVII), (CCCXXXVIII) and (CCCXL) because none of these could accommodate this signal. The downfield shift of C_2 proton was due to the influence of bromine attached to the α-carbon. Another significant three protons singlet at δ 2.4 indicated a methyl group attached to sp^2 carbon and hence suggesting the migration of methyl group from C_{10} to C_1

under the influence of acid during the reaction and also provided further support to the isomeric structure (CCCXXXIX). Signals for remaining methyl protons were observed at δ 1.26, 0.96 and 0.83.

An examination of the IR and the NMR spectra of the compound revealed that most of the spectral properties were found in good agreement with the structure (CCCXXXIX). Thus on the basis of the spectral evaluation the oily substance could best be characterized as 4-aza-A-homo-19-nor-1-methyl-2,6-dibromocholesta-1(10),4a,6-trien-3-one (CCCXXXIX).

Characterization of the compound m.p. 220° as 4-aza-A-homo-19-nor-1-methyl-2,6-dibromocholesta-1,4a,6-trien-3-one (CCCXL)

The compound, m.p. 220° (positive Beilstein test) analysed for $C_{27}H_{39}NOBr_2$. The IR spectrum showed absorption bands at 3500, 3200 (NH), 1670 (—CONH), 1610 (C=C) and 760 cm^{-1} (C-Br).

Since the IR spectral values and elemental analysis were compatible with the four isomeric structures (CCCXXXVII-CCCXL) formulated for the compound. It was NMR spectrum which ultimately proved helpful in arriving at a reasonable conclusion regarding the structure of the compound. It exhibited a broad multiplet for two protons at δ 6.6 attributed to C_{4a}- and C_7-vinylic protons. Another signal for three protons at δ 2.4 (CH_3 at sp^2 carbon) was ascribed to C_1-methyl protons.

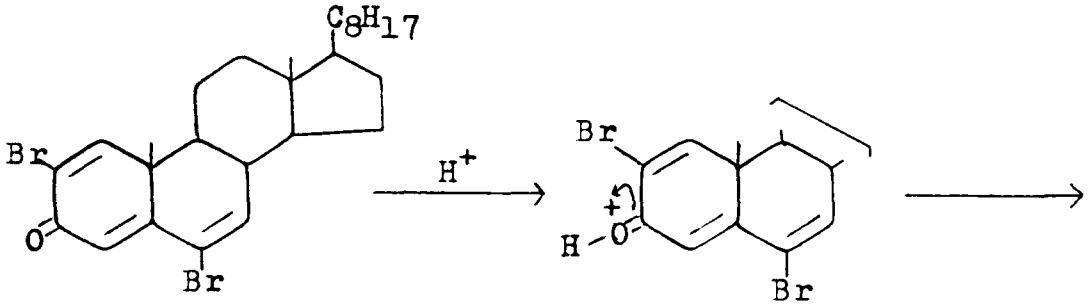
This signal suggested the migration of methyl group from C_{10} to C_1, as discussed during earlier assignment and hence discarded the isomeric structures (CCCXXXVII and CCCXXXVIII). Therefore, the choice of the structure was limited to (CCCXXXIX) and (CCCXL). The careful examination of the NMR spectrum revealed that the spectrum was devoid of any signal for C_2-H at about δ 4.2 so the possibility of the atternate structure (CCCXXXIX) was ruled out. Other methyl signals were observed at δ 1.11, 0.95, and 0.8.

In view of the above observations, it was reasonable to formulate the compound m.p. 220° as 4-aza-A-homo-19-nor-1-methyl-2,6-dibromocholesta-1,4a,6-trien-3-one (CCCXL).

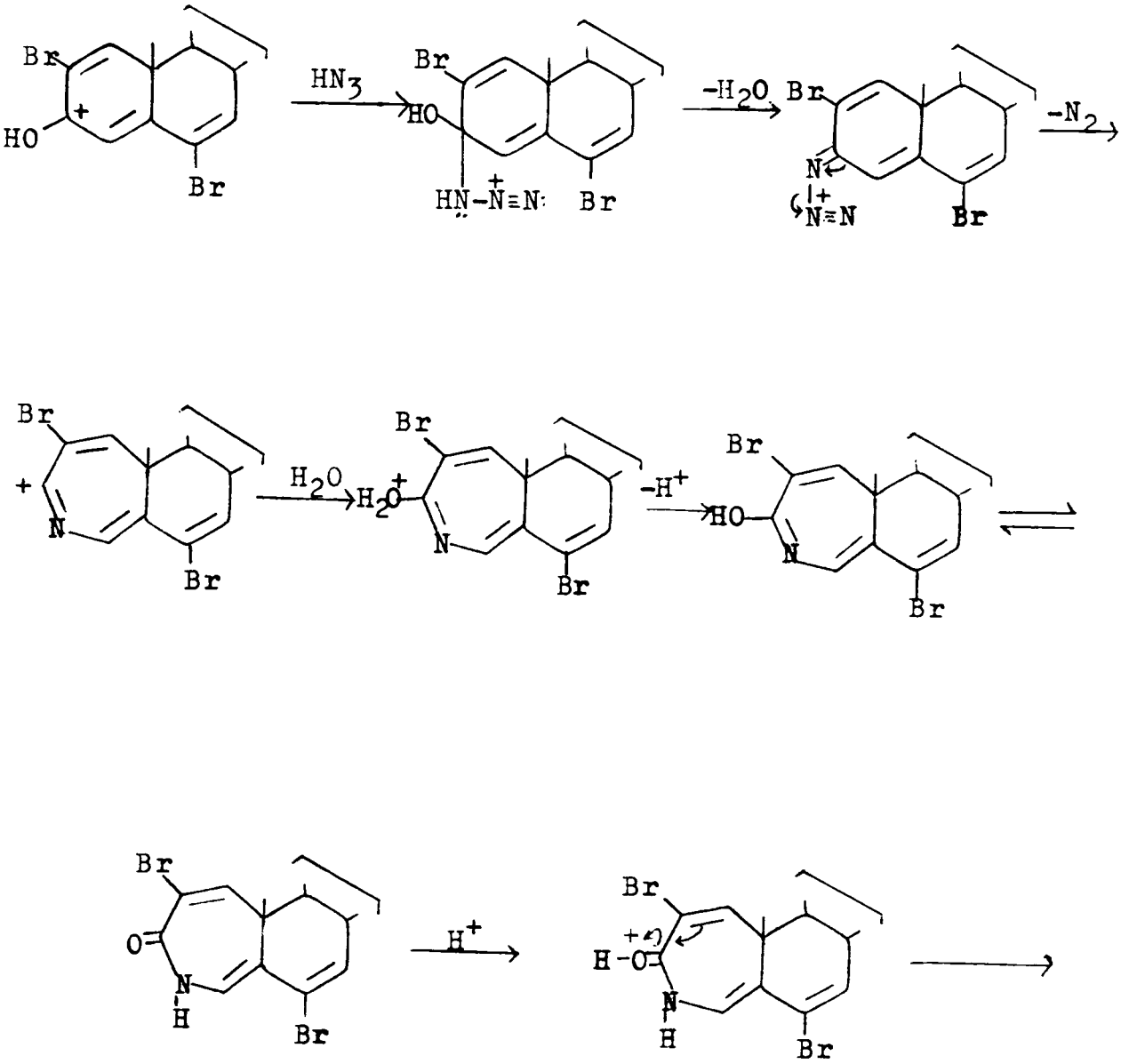
The formation of (CCCXXXIX) and (CCCXL) from the parent ketone (CCCXXXVI) may be shown according to Schemes - VIIA or B.

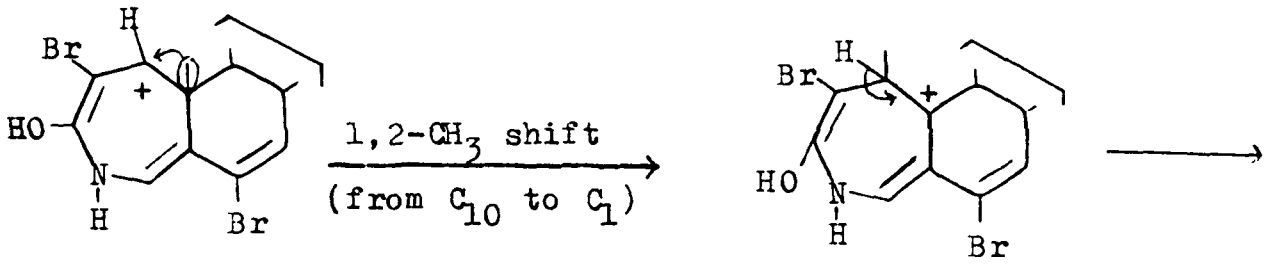
SCHEME - VIIA

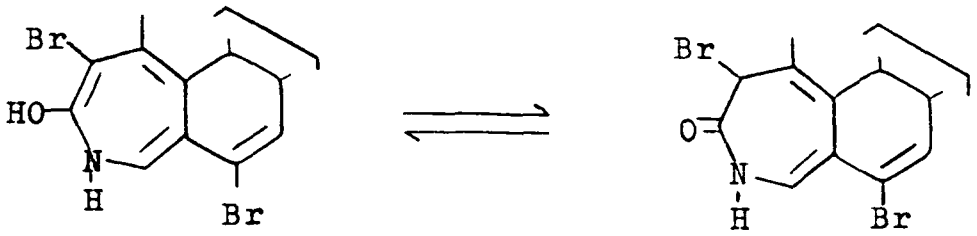
Schmidt reaction of the ketone (CCCXXXVI) followed by 1,2-methyl shift from C_{10} to C_1 under the influence of acid.



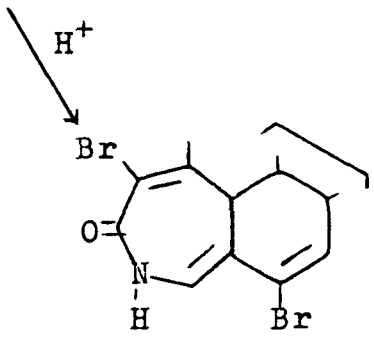
(CCCXXXVI)







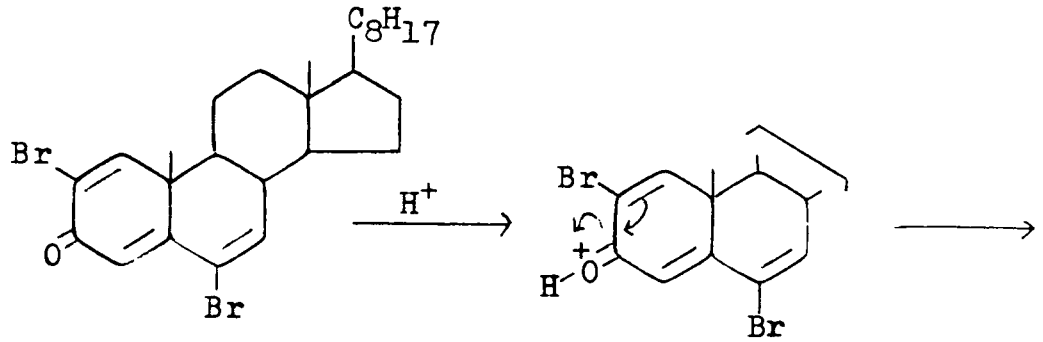
(CCCXXXIX)



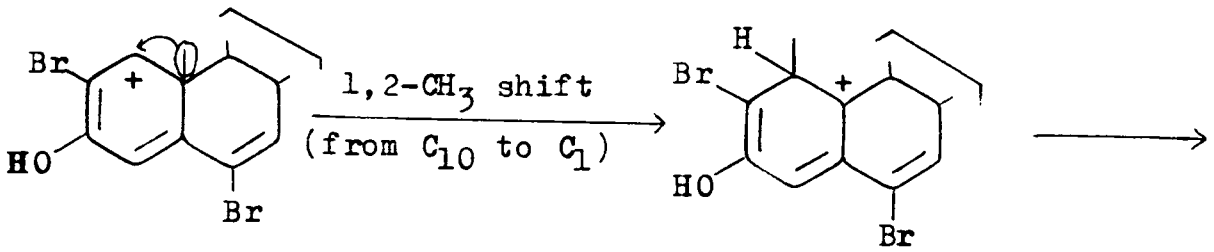
(CCCXL)

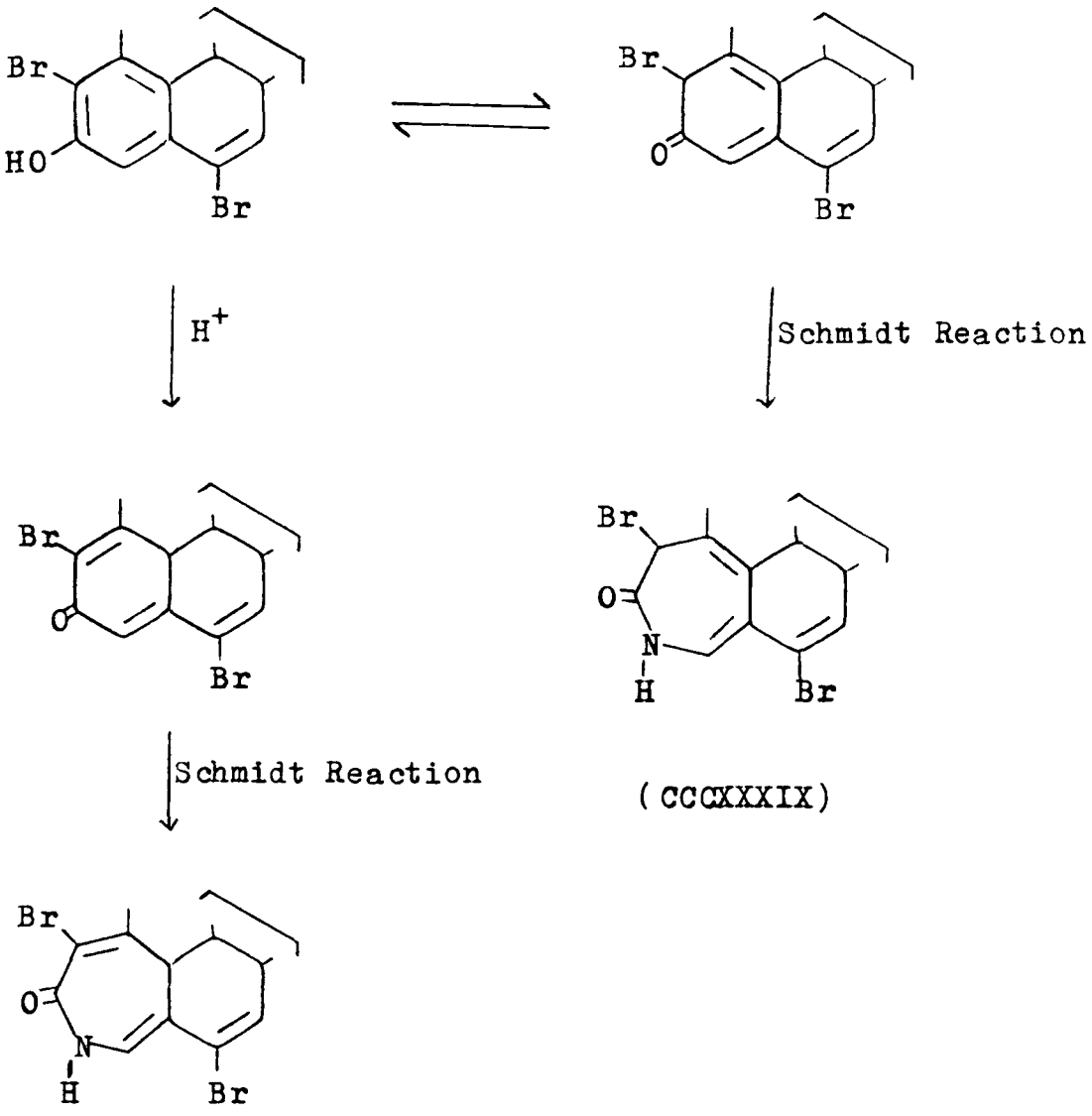
SCHEME - VIIB

1,2-Methyl shift from C_{10} to C_1 of the ketone (CCCXXXVI) under the influence of acid followed by its Schmidt reation.



(CCCXXXVI)





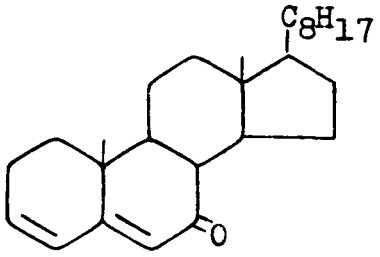
(CCCXXXIX)

(CCCXL)

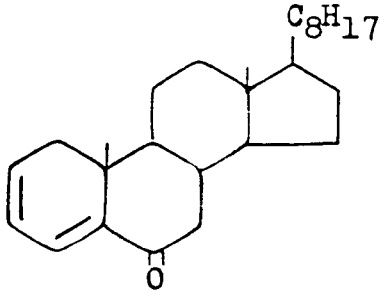
PART - II

TETRAZOLOSTEROIDS

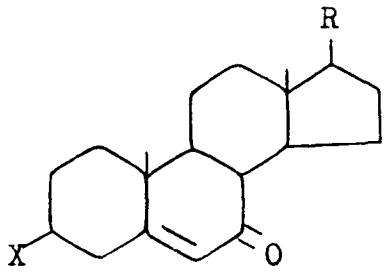
In recent years much attention has been paid towards the formation of steroidal tetrazoles because of the significant biological properties associated with a number of tetrazoles and their use as potential drugs. As a result of this, several papers describing the synthesis of tetrazoles from various steroidal ketones have appeared from our laboratory. These included the reaction of several steroidal ketones, suchas (XXXVIII, CXCIII, CV, CXVIII)[73], (XXVI, XXXIV, CXCVII, CXCIX)[74], (LXXIV, XCII, CXII, CCV)[75], (CXI)[76], (LIV, LVI)[78], (CCXXVI)[79], (CCXXIII, CCXXVIII, CCXXX, CCXXXI, CCXXV, CCXXVI, CXLI)[80].



(CXVIII)



(CXI)



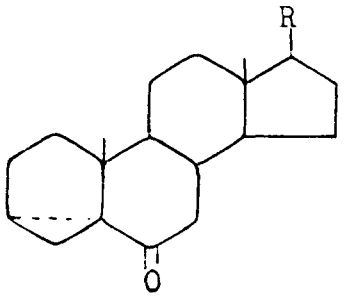
(CV) X, H; R, C_8H_{17}

(CXCIII) X, Cl; R, C_8H_{17}

(CCXXXVI) X, OAc; R, $C_{10}H_{21}$

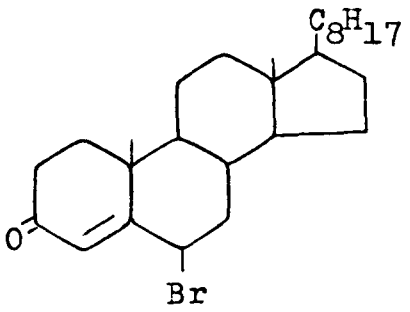
(CCXXXV) X, Cl; R, $C_{10}H_{21}$

(CXLI) X, H; R, $C_{10}H_{21}$

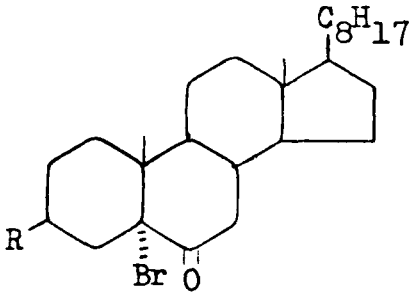


(XXXVIII) R, C_8H_{17}

(CCXXVIII) R, $C_{10}H_{21}$

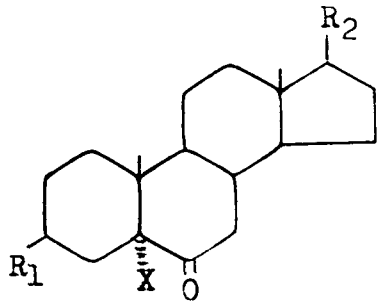


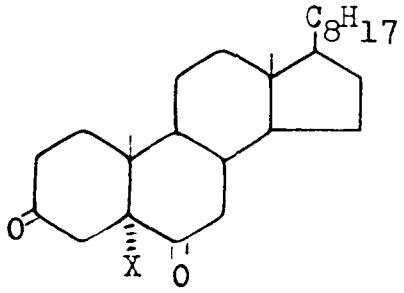
(XCII)



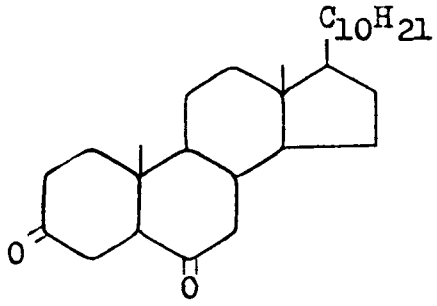
(LVI) R, OH

(LIV) R, OAc

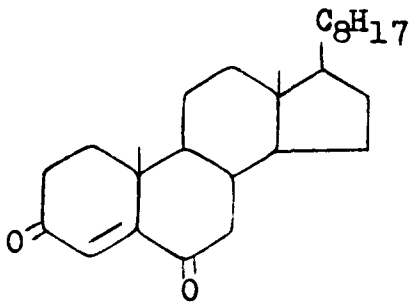




(XXVI)	R_1, H;	X, H;	R_2, C_8H_{17}	(LXXIV)	X, H
(CXCIX)	R_1, OH;	X, H;	R_2, C_8H_{17}	(CCV)	X, OH
(XXXIV)	R_1, OAc;	X, H;	R_2, C_8H_{17}		
(CXCVII)	R_1, Cl;	X, H;	R_2, C_8H_{17}		
(CCXXX)	R_1, OH;	X, H;	R_2, $C_{10}H_{21}$		
(CCXXXI)	R_1, Cl;	X, H;	R_2, $C_{10}H_{21}$		
(CCXXIII)	R_1, OAc;	X, Br;	R_2, $C_{10}H_{21}$		

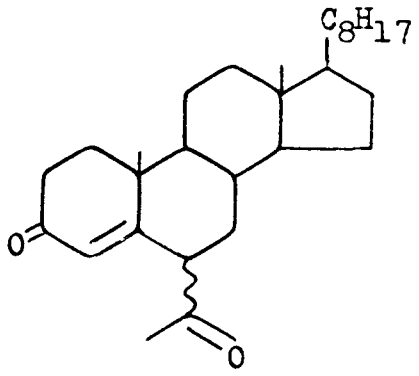


(CCXXVI)

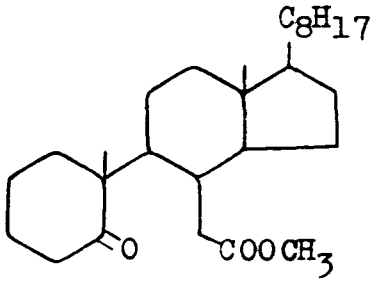


(CXII)

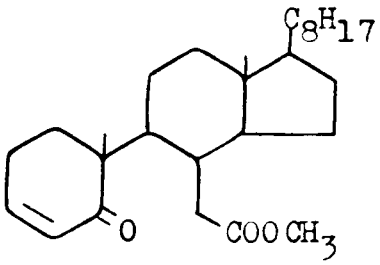
This chapter is an extension of the above work on the synthesis of tetrazoles from the cholestane series. It describes the reaction of easily accessible steroidal ketone 6ξ-acetylcholest-4-en-3-one (CCCXXIV) and seco-keto esters like methyl 5-keto-5,6-secocholestan-6-oate (CCCXLV) and methyl 5-keto-5,6-secocholest-3-en-6-oate (CCCXLVIII) with an excess of hydrazoic acid in the presence of boron trifluoride as the catalyst, a varient of the Schmidt reaction.



(CCCXXIV)



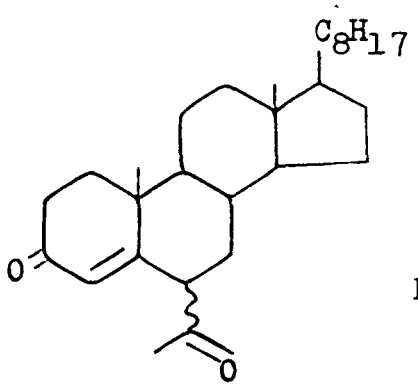
(CCCXLV)



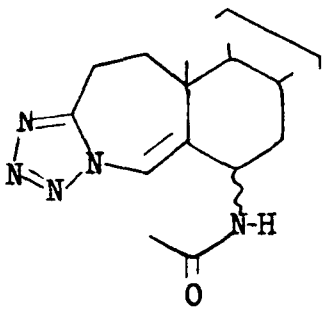
(CCCXLVIII)

Reaction of 6ξ-Acetylcholest-4-en-3-one (CCCXXIV) with an excess of hydrazoic acid

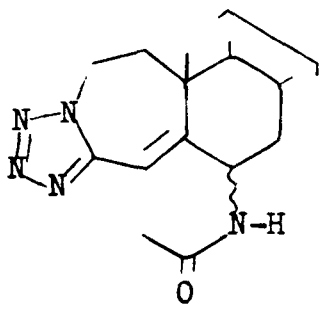
6ξ-Acetylcholest-4-en-3-one (CCCXXIV) was treated with an excess of hydrazoic acid solution (prepared according to the method described by Moural and Syhora)[65] in the presence of boron trifluoride etherate. Usual workup of the reaction mixture and column chromatography over silica gel provided two products m.p. 289° and 278°.



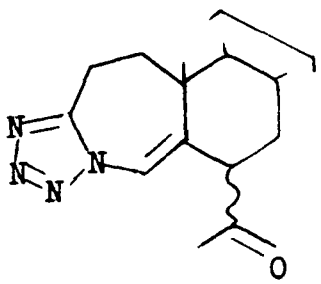
(CCCXXIV)



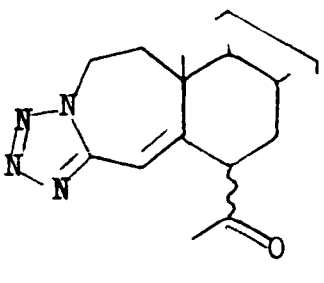
(CCCXLI)



(CCCXLII)



(CCCXLIII)

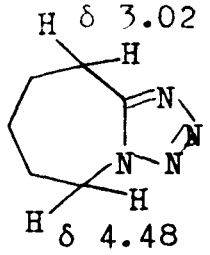


(CCCXLIV)

Characterization of the compound m.p. 289° as 6β-N-acetamido-3-aza-A-homocholest-4a-eno[3,4-d]tetrazole (CCCXLII)

The compound m.p. 289° analysed for $C_{29}H_{47}N_5O$. This molecular composition indicated the addition of five nitrogen atoms to the starting ketone (CCCXXIV) hence both the keto groups of the substrate had been affected during the reaction. The IR spectrum of the compound showed absorption bands at 3280, 1650, 1525, 1450 and 1370 cm^{-1}. The band at 3280 was assigned to NH stretching whereas the band at 1650 cm^{-1} was attributed to CONH function. In the light of the earlier observation[66] the band at 1525 cm^{-1} was ascribable to C=N frequency and those at 1450 and 1370 cm^{-1} were due to N=N stretching. The elemental analysis and IR values of the compound m.p. 289° suggested the presence of an amide group and a tetrazole moiety, and therefore two isomeric structures (CCCXLI snd CCCXLII) could be formulated for this compound. The conclusive distinction between the two isomers was done on the basis of its NMR spectrum.

Di Maio and Permutti reported that the NMR spectrum of the tetrazole (CXVII)[116] showed a two protonsmultiplet at δ 4.48 which was assigned to the methylene group directly attached to the ring nitrogen atom and other two protons multiplet at δ 3.02 due to the methylene group adjacent to C=N fragment of the tetrazole system.



(CXLVII)

The NMR spectrum of the compound m.p. 289° exhibited a singlet at δ 6.96 integrating for one proton was assigned to C_{4a}-vinylic proton. This downfield shift of C_{4a}-vinylic proton was due to the influence of neighbouring C=N fragment of the tetrazole system as in the structure (CCCXLII). The broad signal for one proton at δ 5.15 was due to the amido proton [disappeared after D_2O shake]. In addition to these signals, other significant two protons multiplet observed at δ 4.5 was ascribable to C_2-methylene protons. This observation was compatible with the structure (CCCXLII) hence the alternate structure (CCCXLI) could be discarded because in that case the C_2-protons would have appeared at about δ 3.2. The signal at δ 3.0 ($W_{\frac{1}{2}}$ 9 Hz) for one proton was assigned to C_6-$\underline{H}$ whereas the singlet for three protons at δ 2.04 was attributed to methyl protons of $\underline{CH_3}$-C(=O)-NH- grouping. Remaining methyl signals were observed at δ 1.86, 1.16, 0.9 and 0.8.

On the basis of the above spectral evaluation the compound m.p. 289° can be characterized as 6β-N-acetamido-3-aza-A-homocholest-4a-eno[3,4-d]tetrazole (CCCXLII).

Characterization of the compound m.p. 278° as 6ξ-acetyl-3-aza-A-homocholest-4a-eno[3,4-d]tetrazole (CCCXLIV)

The compound analysed for $C_{29}H_{46}N_4O$ and thus the formation of a tetrazole was evident from its elemental analysis. Its IR spectrum showed bands at 1705, 1530, 1460 and 1380 cm^{-1}. The band at 1705 cm^{-1} was attributed to carbonyl function of acetyl group. The other significant band at 1530 was due to C=N frequency and those at 1460 and 1380 cm^{-1} were ascribable to N=N stretching.

The molecular composition and IR values of the compound m.p. 278° suggested that during the reaction one of the two carbonyl groups of the substrate (CCCXXIV) remained unaffected, therefore two isomeric structures (CCCXLIII and CCCXLIV) could be written for the compound. A clear distinction between the two isomers was made possible with the help of its NMR spectrum which exhibited one proton singlet at δ 6.5 assigned to C_{4a}-vinylic proton, as discussed during earlier assignment. The downfield shift of C_{4a}-vinylic proton was due to the influence of neighbouring C=N fraction of the tetrazole system compatible with the structure (CCCXLIV) only. Further the spectrum was devoid of any amido proton signal. The appearance of C_2-methylene protons at δ 4.2 suggested the attachment of ring nitrogen directly to the C_2-methylene group and hence provided further support to the structure

(CCCXLIV). Therefore, in the light of the above spectral evidences the alternative structure (CCCXLIII) could be discarded. The signal at δ 3.1 ($W_{\frac{1}{2}}$ 8 Hz) was due to C_6-$\underline{6}H$. The signal for methyl protons of acetyl group was observed at δ 2.01. Remaining methyl signals were obtained at δ 1.25, 0.97, 0.9, 0.76 and 0.7.

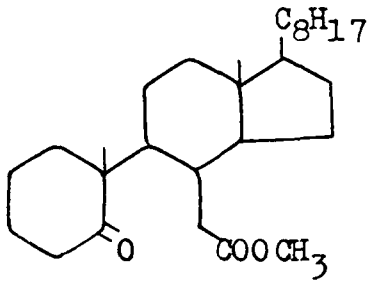
On the basis of the preceding discussion the compound, m.p. 278° may be characterized as 6ξ-acetyl-3-aza-A-homo-cholest-4a-eno[3,4-d]tetrazole (CCCXLIV).

Reaction of Methyl 5-keto-5,6-secocholestan-6-oate (CCCXLV) with an excess of hydrazoic acid : Methyl 5,6-seco-4a-aza-A-homocholestan[5a,5-d]tetrazole-6-oate (CCCXLVII)

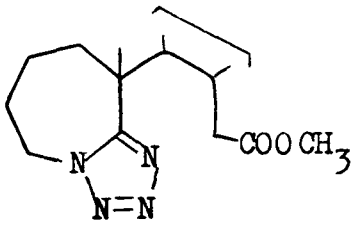
Methyl 5-keto-5,6-secocholestan-6-oate (CCCXLV) was prepared for the present study following literature procedure[117]. [ν_{max} 1735 ($\underline{C}OOCH_3$), 1708 (C=O); δ(100 MHz), 3.56 s(3 protons, $COOC\underline{H}_3$), 2.2 umc(4 protons, $CO-C\underline{H}_2$ and $C\underline{H}_2-COOCH_3$), 1.0 s(3 protons, $C_{10}-C\underline{H}_3$), 0.9, 0.83 and 0.68 (other methyl groups). The spectral data for the seco ester (CCCXLV) were obtained for total identification and comparison purpose.

The ester (CCCXLV) was treated with an excess of hydrazoic acid solution in the presence of boron trifluoride. Usual work-up of the reaction mixture and subsequent column chromatography

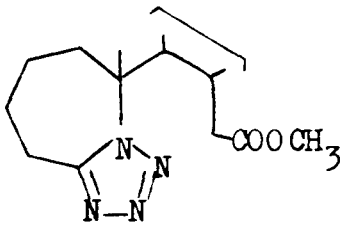
over silica gel furnished a single product, m.p. 148° which analysed for $C_{28}H_{48}N_4O_2$.



(CCCXLV)



(CCCXLVI)



(CCCXLVII)

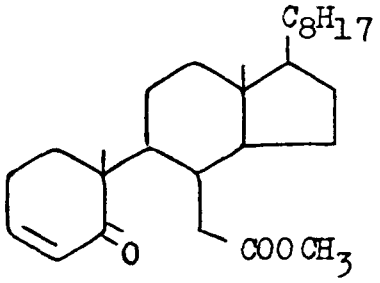
From the molecular composition it was evident that four nitrogen atoms have been added during the course of the reaction and therefore, suggested two obvious structural possibilities (CCCXLVI and CCCXLVII). A distinction between the two was obtained by spectral properties. The IR spectrum showed bands at 1730 ($\underline{C}OOCH_3$), 1520 (C=N), 1460 and 1375 cm^{-1} (N=N) which incidently supported both the structures (CCCXLVI and CCCXLVII) equally well. The NMR spectrum was much more revealing and it gave signals at δ 3.31 s(3 protons), 3.08 m (2 protons), 2.8 m(2 protons), 1.78 s(3 protons), 1.18, 0.91, 0.8 and 0.7 (other methyl protons). The singlet at δ 3.31 was assigned to an ester methyl group ($COOC\underline{H}_3$) and the multiplet centred at δ 3.08 was ascribable to C_4-$\underline{H}_2$. The appearance of C_4-methylene protonsat δ 3.08 suggested that the C=N fragment of the tetrazole system was adjacent to C_4-methylene·

group[116]. This observation was compatible with the structure (CCCXLVII) only and hence discarded the alternative (CCCXLVI). Another multiplet observed at δ 2.8 was due to C_7-methylene protons. The singlet at δ 1.78 was assigned to C_{10}-C$\underline{H}_3$. This downfield shift of C_{10}-C$\underline{H}_3$ signal clearly indicated that grouping -N-C-CH_3 was present in the compound, and provided further support to the structure (CCCXLVII). On the other hand the isomeric structure (CCCXLVI) would have given a signal at δ 4.4 for C_4-$\underline{H}_2$, i.e., for the grouping -C$\underline{H}_2$-N-. Further, the C_{10}-C$\underline{H}_3$ signal in (CCCXLVI) was not likely to suffer such a downfield shift. The NMR spectrum thus supported the structure (CCCXLVII).

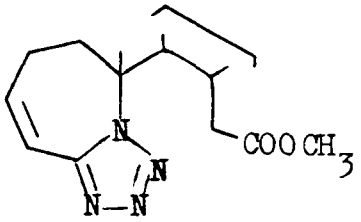
Reaction of Methyl 5-keto-5,6-secocholest-3-en-6-oate (CCCXLVIII) with an excess of hydrazoic acid : Methyl 5,6-seco-4a-oxo-5-aza-A-homocholest-3-en-6-oate (CCCLII)

Methyl 5-keto-5,6-secocholest-3-en-6-oate (CCCXLVIII) was prepared for the present study according to the literature procedure[118]. [ν_{max} 3040 (C=C-$\underline{H}$), 1735 (COOCH_3), 1675 (C=C-C=O), 1615 (C=C) and 1165 cm^{-1} (methyl ester); δ 6.75 m (C_3-$\underline{H}$), 5.8 d(C_4-$\underline{H}$), 3.57 s(C$\underline{H}_3$-COO), 2.8 m(C_7-2$\underline{H}$), 1.07 (C_{10}-C$\underline{H}_3$), 0.88, 0.8 and 0.66 (other methyl groups)]. The spectral data for the seco ester (CCCXLVIII) were obtained for total identification and comparison purpose.

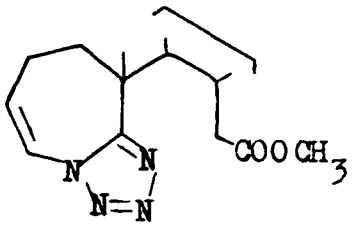
The ester (CCCXLVIII) was treated with an excess of hydrazoic acid in the usual manner. Workup of the reaction mixture and column chromatography over silica gel afforded single compound, m.p. 184° which analysed for $C_{28}H_{47}NO_3$.



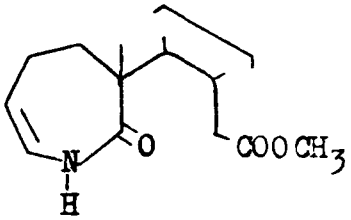
(CCCXLVIII)



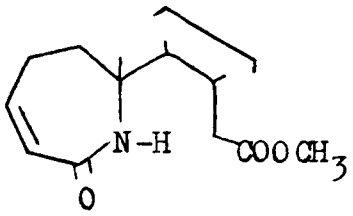
(CCCXLIX)



(CCCL)



(CCCLI)



(CCCLII)

Since it was evident from the molecular composition that during the course of reaction only one nitrogen atom was added to the substrate therefore the possibilities of the tetrazole structures (CCCXLIX and CCCL) was ruled out in favour of the lactams (CCCLI) and (CCCLII).

The IR spectrum gave bands at 3400, 3140 (N-H), 1740 ($\underline{COO}CH_3$), 1675 (CONH) and 1640 cm^{-1} (C=C) and these values supported both the probable structures (CCCLI and CCCLII). A clear distinction between the two isomers was made possible with the help of its more informative NMR spectrum which exhibited signals at 7.15 br(1 proton), 5.7 br,m(1 proton), 4.7 br m(1 proton), 3.5 s(3 protons), 2.5 m(4 protons), 1.2 s (3 protons), 0.9, 0.8 and 0.6 (remaining methyl protons).

The broad signal at δ 7.15 integrating for 1 proton (disappeared on D_2O shake) was assigned to CO-N$\underline{H}$ group . Another signal as broad multiplet at δ 5.7 integrating for one proton was ascribable to C_3-vinylic proton (β to C=O) and the other singlet at δ 4.7 was assigned to C_4-vinylic proton. A singlet observed at δ 3.5 was due to methyl protons of ester function. A broad multiplet at δ 2.5 integrating for four protons was assigned to C_2-$\underline{H}_2$ and C_7-$\underline{H}_2$. The C_{10}-$C\underline{H}_3$ signal appeared at δ 1.2. The other methyl signals were observed at δ 0.9, 0.8 and 0.6.

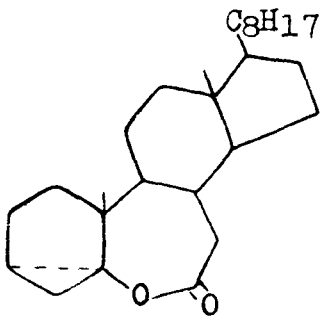
Therefore on the basis of the foregoing discussion the compound, m.p. 184^{o} could be characterized as methyl 5,6-seco-4a-oxo-5-aza-A-homocholest-3-en-6-oate (CCCLII).

PART - III

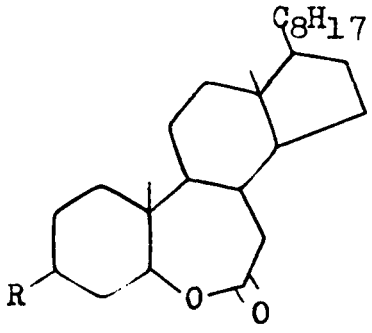
OXASTEROIDS

Baeyer-Villiger oxidation of steroidal ketones is the most elegant method for the insertion of oxygen atom into the steroidal framework.

Previous work from our laboratory had described the Baeyer-Villiger oxidation of several steroidal ketones in order to prepare oxasteroids of probable biological potentials. The work was mainly concerned with the cholestane and the stigmastane series and as a result, a large number of the then unknown oxasteroids were synthesized. These oxasteroids are (CCXLIV, CCXLV, CCXLVII, CCXLVIII)[84], (CCXLV, CCXLIX, CCL, CCLI, CCLII, CCLIII, CLIV, CCLV)[86], (CCLVI, CCLVII , CCLVIII, CCLIX, CCLX, CCLXI)[87], (CCLXIII, CCLXVI)[88], (CCLXVII)[89], (CCLXXIV)[94], (CCLXXVI)[95], (CCLXXXIII)[96], (CCXCIII, CCXCIV)[98] and (CCCII)[99].



(CCXLIV)



(CCXLV) R, Cl

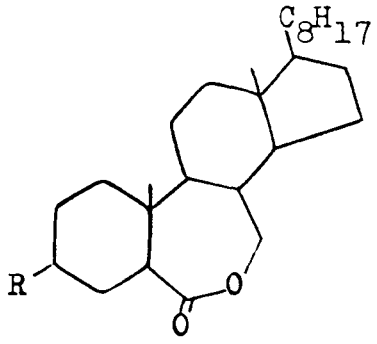
(CCXLVII) R, Br

(CCXLVIII) R, I

(CCXLIX) R, OAc

(CCL) R, OH

(CCLI) R, H

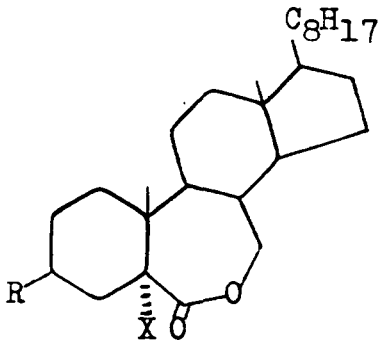


(CCLII) R, OAc

(CCLIII) R, OH

(CCLIV) R, Cl

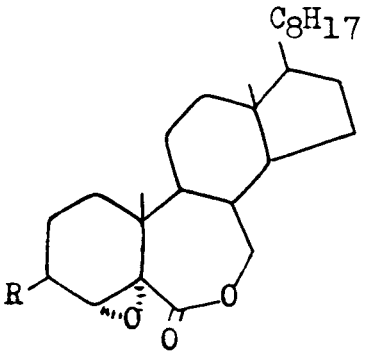
(CCLV) R, H



(CCLVII) X, Br; R, H

(CCLXI) X, Br; R, OH

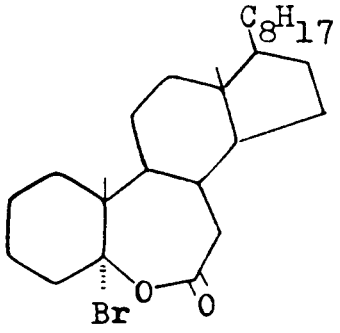
(CCLXIII) X, OH; R, OAc



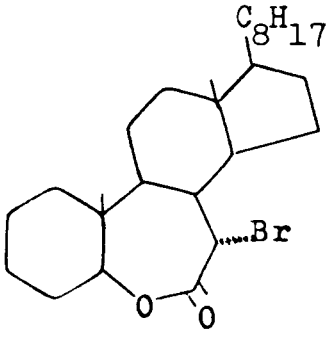
(CCLIX) R, OH

(CCLX) R, OBz

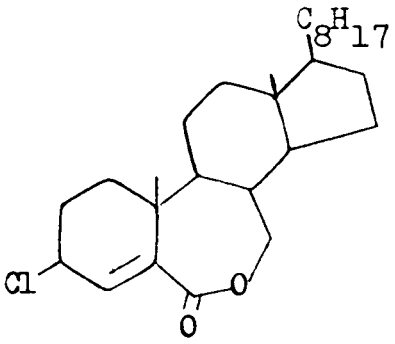
(CCLXXXIII) R, H



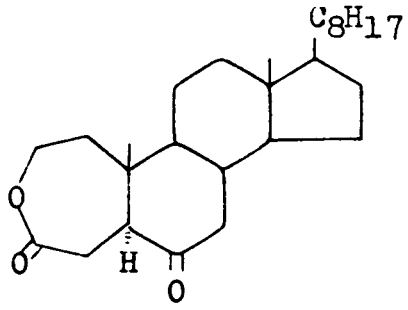
(CCLVI)



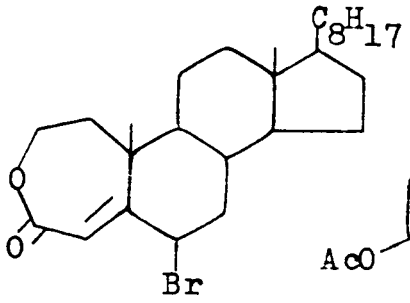
(CCLVIII)



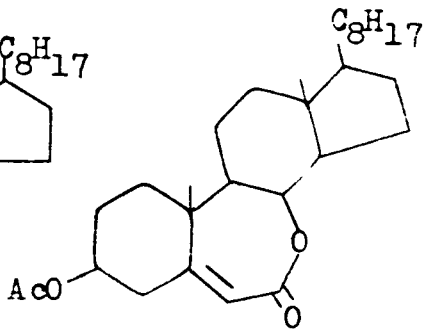
(CCLXVI)



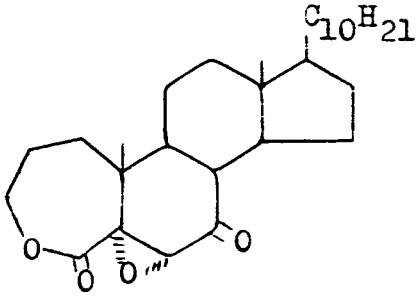
(CCLXVII)



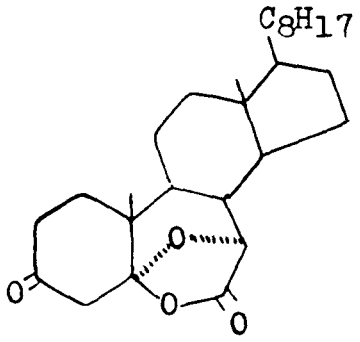
(CCLXXIV)



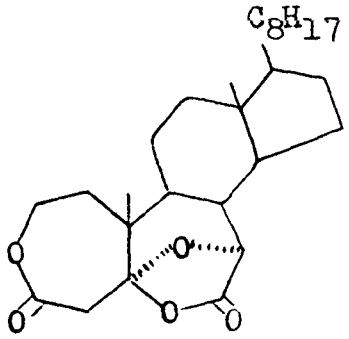
(CCLXXVI)



(CCCII)

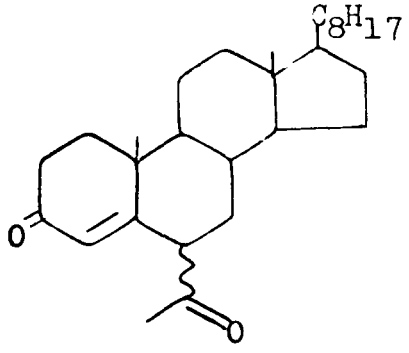


(CCXCIII)

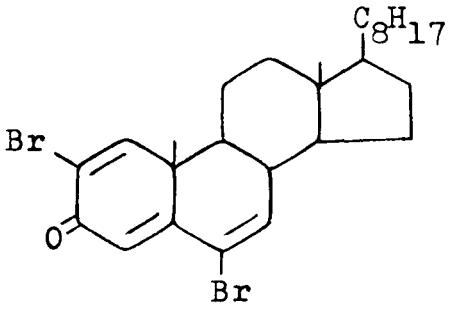


(CCXCIV)

As an extension of the above work, steroidal ketones suchas 6ξ-acetylcholest-4-en-3-one (CCCXXIV) and 2,6-dibromocholesta-1,4,6-trien-3-one (CCCXXXVI) were subjected to the Baeyer-Villiger oxidation in order to get the corresponding oxasteroids. The characterization of the products thus obtained was done on the basis of their spectral properties.



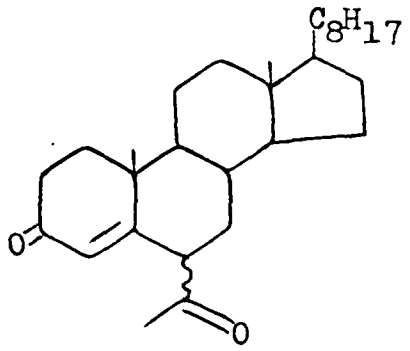
(CCCXXIV)



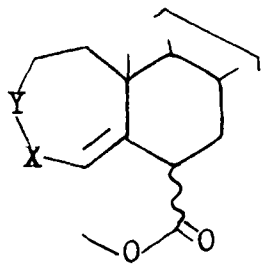
(CCCXXXVI)

Baeyer-Villiger oxidation of 6ξ-Acetylcholest-4-en-3-one (CCCXXIV)

6ξ-Acetylcholest-4-en-3-one (CCCXXIV) was treated with a chloroform solution of perbenzoic acid (2.5 mole equivalent) and p-toluenesulphonic acid monohydrate as catalyst for 96 hours at room temperature. The progress of the reaction was monitored by t.l.c. of the reaction mixture from time to time. The usual workup of the reaction mixture and subsequent column chromatography over silica gel furnished two non-crystallizable products referred to as B_1 and B_2, respectively.

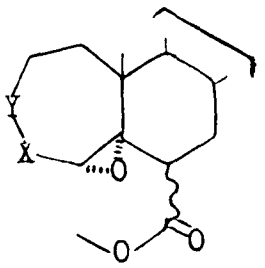


(CCCXXIV)



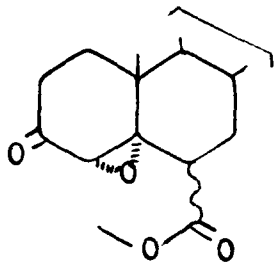
(CCCLIII) X, O; Y, CO

(CCCLIV) X, CO; Y, O



(CCCLV) X, O; Y, CO

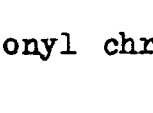
(CCCLVI) X, CO; Y, O



(CCCLVII)

Characterization of the oil B_1 as methyl 4α,5-epoxy-5α-cholestan-3-oxo-6ξ-carboxylate (CCCLVII)

The oil B_1 obtained as a non crystallizable oil analysed for $C_{29}H_{46}O_4$. The molecular composition of the compound revealed that two oxygen atoms had been added to the substrate (CCCXXIV) during the course of reaction and this could lead to several structural possibilities, suchas, (CCCLIII), (CCCLIV) and (CCCLVII).

The IR spectrum gave significant bands at 1740 ($COOCH_3$), 1705 (C=O) and 910 cm^{-1} (epoxide). These spectral values narrowed down the choice to only the epoxy structure (CCCLXXIV) as others would have shown different values having ε-lactone, ε-enollactone and/or α,β-unsaturated carbonyl moieties. The NMR spectrum was devoid of any vinylic proton signal required for the structures (CCCLIII) and (CCCLIV) and hence provided further support to the epoxy structure (CCCLVII). Another signal at δ 3.8 integrating for one proton was ascribable to the $C_4\beta$-proton. This lower field appearance, was it self suggestive of the fact that there was a proton attached to epoxy ring adjacent to a carbonyl chromophore ().

Further a three proton singlet observed at δ 3.6 was due to the methyl protons of ester function. A broad signal obtained at δ 2.03 integrating for two protons was assigned to C_2-methylene protons and $C_6\xi$-proton signal appeared as a multiplet at δ 3.3 ($W_{\frac{1}{2}}$ 9 Hz). Remaining methyl protons signals were observed at δ 1.2, 1.16, 0.95, 0.85 and 0.71.

The formation of the compound as an α-epoxide had been suggested on the general understanding that the reaction occurs from the less sterically hindered α-side (back side) of the steroidal molecule. On the basis of the foregoing discussions and spectral values, the oily compound B_1 could

be characterized as methyl 4α,5-epoxy-5α-cholestan-3-oxo-6ξ-carboxylate (CCCLVII).

Characterization of the oily compound B_2 as methyl 3-oxo-4aα, 5-epoxy-A-homo-5α-cholestan-4-oxa-6ξ-carboxylate (CCCLV)

The oily product analysed for $C_{29}H_{46}O_5$. It was evident from the elemental analysis that three atoms of oxygen were introduced during the reaction. Introduction of three oxygen atoms to the substrate (CCCXXIV) could lead to two obvious structural possibilities (CCCLV) and (CCCLVI).

The IR spectrum showed two distinct bands at 1750 (broad) and 910 cm^{-1}. The broad band at 1750 was ascribable to atleast two carbonyl groups, an ester function and epoxy lactone moiety, where as the medium band for an epoxy ring was observed at 910 cm^{-1}. These values supported both the isomeric structures (CCCLV) and (CCCLVI).

The conclusive distinction between the two possible isomers was made possible with the help of its NMR spectrum which exhibited signals at δ 4.0(1 proton), 3.5 (3 protons), 3.1 (1 proton), 2.56(2 protons), 1.38, 1.28, 1.2, 0.8 and 0.7 (methyl protons).

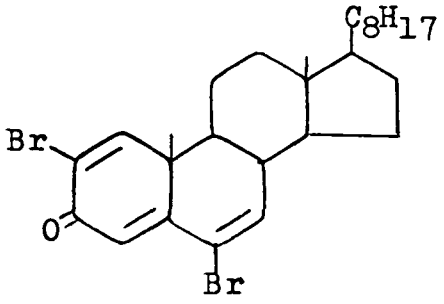
The broad signal at δ 2.56 was ascribable to C_2-methylene protons compatible with the structure (CCCLV) only, since

the alternate structure (CCCLVI) required its appearance at lower field. A three protonssinglet observed at δ 3.5 could easily be assigned to the methyl protons of ester function. Another signal at δ 4.0 was due to C_{4a}-β proton. The down-field appearance of C_{4a}β-proton was due to its attachment to an epoxy carbon adjacet to an oxygen atom. This observation provided further support to the structure (CCCLV). The broad signal for C_6ξ-proton was observed at δ 3.1 ($W_{\frac{1}{2}}$ 8 Hz).

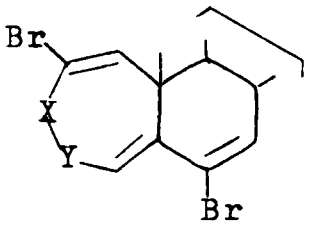
Thus on the basis of preceding discussion and spectral evaluation the compound B_2 could be characterized as methyl 3-oxo-4aα,5-epoxy-A-homo-5α-cholestan-4-oxa-6ξ-carboxylate (CCCLV).

<u>Reaction of 2,6-Dibromocholesta-1,4,6-trien-3-one (CCCXXXVI) with perbenzoic acid : 6,7α-Oxido-2,6-dibromocholesta-1,4-dien-3-one (CCCLXII-a)</u>

Oxidation of 2,6-dibromocholesta-1,4,6-trien-3-one (CCCXXXVI) with 2.5 mole of perbenzoic acid (p-toluene--sulphonic acid monohydrate as catalyst) provided a single compound, m.p. 145° which analysed for $C_{27}H_{38}O_2Br_2$.

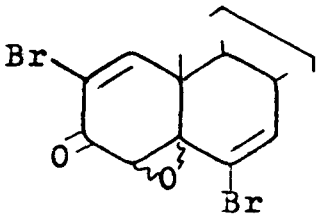


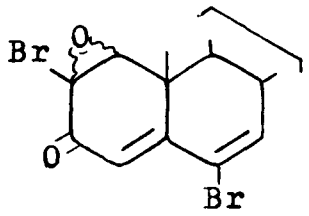
(CCCXXXVI)

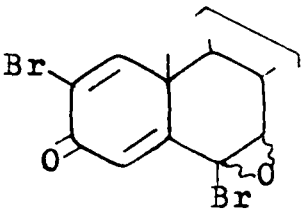


(CCCLVIII) X, O; Y, CO

(CCCLIX) X, CO; Y, O







(CCCLX-a) α, epoxy (CCCLXI-a) α, epoxy (CCCLXII-a) α, epoxy

(CCCLX-b) β, epoxy (CCCLXI-b) β, epoxy (CCCLXII-b) β, epoxy

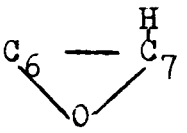
The molecular composition of the compound supported the addition of one oxygen atom to the substrate (CCCXXXVI) during the reaction. This observation suggested various stuructural possibilities (CCCLVIII), (CCCLIX), (CCCLX-a/b), (CCCLXI-a/b) and (CCCLXII-a/b) for the compound.

The IR spectrum exhibited absorption bands at 1685, 1610, 910 and 760 cm^{-1}. The sharp band at 1690 was due to α,β-unsaturated ketone moiety whereas the olefinic band was observed at 1610 cm^{-1}. The characteristic band for epoxide was noted at 910 cm^{-1}. The band for C-Br linkage was at 760 cm^{-1}. Apparently there was no band compatible with lactone structures.

The IR spectral band at 910 cm^{-1} for epoxide accounts for the added oxygen and thus the possibilities for ε-lactone structures (CCCLVIII) and (CCCLIX) were ruled out in favour of the epoxides (CCCLX-a/b), (CCCLXI-a/b) and (CCCLXII-a/b).

The conclusive differentiation between several isomeric epoxides were done with the help of its NMR spectrum. It showed signals at δ 7.1 s(1 proton), 6.75 s(1 proton), 3.48 br (1 proton), 1.3 s(3 protons), 0.9, 0.8 and 0.75 (remaining methyl protons).

In a multiple unsaturated substrate suchas (CCCXXXVI) it was essential to locate the epoxy group in the product. There are two C=C (double bonds) in the ring A as a crossed conjugated dienone system, where as the remaining double bond is located in ring B (C_6-C_7). Addition of one oxygen on to the substrate (epoxide formation) could lead to three regional possibilities (CCCLX-a/b), (CCCLXI-a/b) and (CCCLXII-a/b)

The NMR spectrum of the product and its comparison with the substrate very clearly revealed that epoxidation has occurred at C_6-C_7 double bond. The singlet at δ 7.1(C_1-vinylic proton) and δ 6.75 (C_4-vinylic proton) leave no doubt that the reacting site is C_6-C_7. That the epoxy ring is α-oriented is further revealed by broad singlet at δ 3.48 () which

is ascribed to C_7-β<u>H</u> (equatorial). The broad singlet (non split signal) shows that the dihedral angle between C_8 axial - H (β) and C_7 equatorial - H (β) is about 90°. The structure of the compound m.p. 145° should be 6,7α-oxido-2,6-dibromo-cholesta-1,4-dien-3-one (CCCLXII-a).

PART - IV

MASS SPECTRAL STUDIES ON STEROIDAL NITROOLEFINS

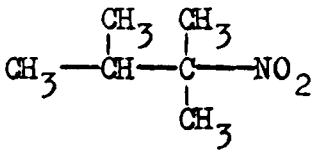
During recent past, the mass spectra of several nitro compounds have been measured. One of the most important processes in the mass spectrometry of nitro compound is the loss of a NO_2 radical and the subsequent decomposition of the alkyl fragment. Another process is the loss of both the oxygen atoms to yield the equivalent of a nitrile species. The mass spectra of aromatic nitro compounds show a primary loss of O, NO and NO_2 and the formation of NO^+.

Djerassi et al.[119] have carried out the mass spectral studies on nitromethane (CCCLXIII) and nitroethane (CCCLXIV). A detailed examination of the mass spectra of 1-nitropropane (CCLXV) and its deuterated analogues[120] (CCLXVa-c) has been carried out in an attempt to rationalize the genesis of different fragment ions in nitroalkanes.

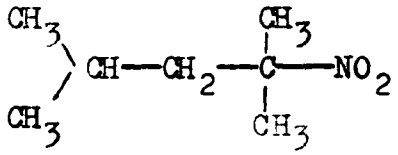
$CH_3 - NO_2$	$CH_3-CH_2-NO_2$	$CH_3-CH_2-CH_2-NO_2$
(CCCLXIII)	(CCCLXIV)	(CCCLXV)

$CH_3CH_2-CD_2-NO_2$	$CH_3CD_2CH_2-NO_2$	$CD_3CH_2CH_2-NO_2$
(CCCLXV-a)	(CCCLXV-b)	(CCCLXV-c)

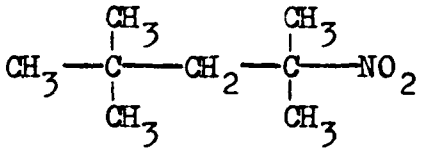
The mass spectra of several tertiary nitroalkanes[119] suchas 2,3-dimethyl-2-nitrobutane (CCCLXVI), 2,4-dimethyl-2-nitropentane (CCCLXVII) and 2,4,4-trimethyl-2-nitropentane (CCCLXVIII) have been examined. The main feature is the loss of HNO_2 from the molecular ion giving the highest discernible peak in various spectra.



(CCCLXVI)

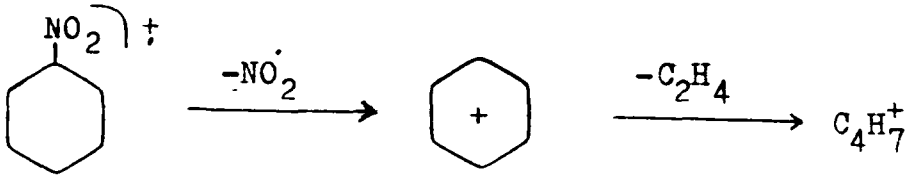


(CCCLXVII)



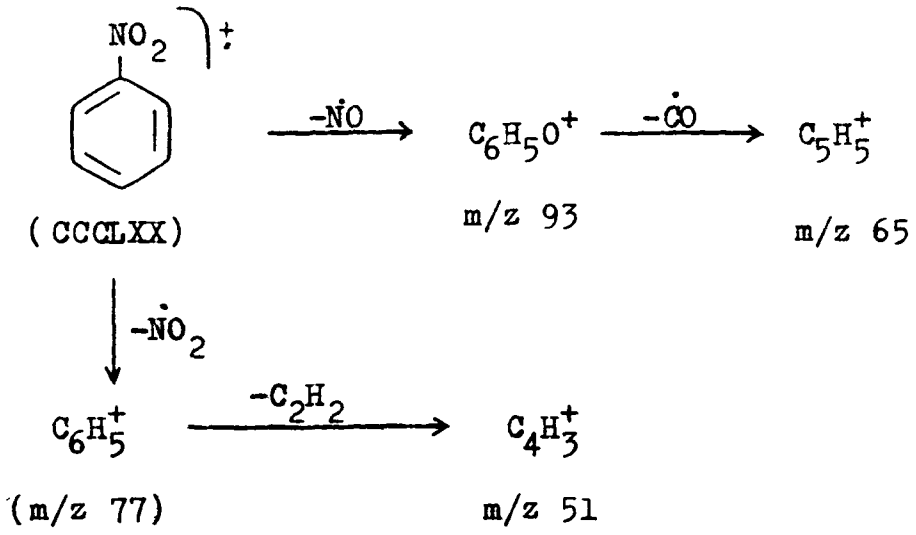
(CCCLXVIII)

The mass spectra of some alicyclic nitro compounds[119] have been studied. In nitrocyclohexane (CCCLXIX), for example, an ion formed by the loss of NO_2 is responsible for the most intense peak at m/z 83. The cyclohexyl cation decomposes further by the expulsion of ethylene to give $C_4H_7^+$ (m/z 55).

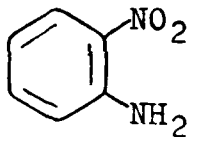


(CCCLXIX) m/z 83 m/z 55

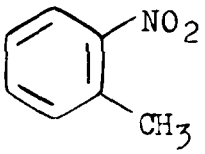
The mass spectra of aromatic nitro compounds shows the primary loss of O, NO and NO_2. The mass spectrum of nitrobenzene (CCCLXX)[121] reveals an intense molecular ion peak while the base peak corresponds to $C_6H_5^+$ (m/z 77), due to the loss of NO_2. The most interesting fragment is the one at m/z 93, resulting from a rearrangement with the loss of NO in a one step process[122]. The m/z 93 ion thus corresponds to phenoxy cation ($C_6H_5O^+$) from which the $C_5H_5^+$ ion may arise due to the ejection of CO.



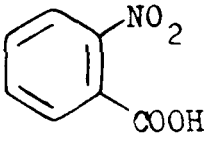
In order to study the substituent effect on the mass spectra of nitroarenes a number of compounds suchas nitroaniline (CCCLXXI)[123-125], o-nitrotoluene (CCCLXXII)[126,127], o-nitrobenzoic acid (CCCLXXIII)[128], o-nitroacetophenone (CCCLXXIV)[128], o-nitrobenzamide (CCCLXXV)[128] and o-nitroacetanilide (CCCLXXVI)[128] have been examined in detail.



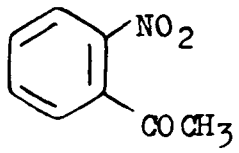
(CCCLXXI)



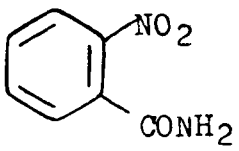
(CCCLXXII)



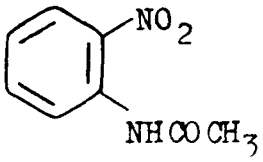
(CCCLXXIII)



(CCCLXXIV)

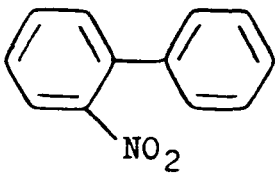


(CCCLXXV)



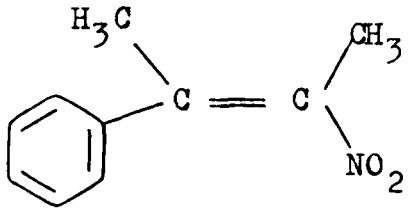
(CCCLXXVI)

The mass spectrum of nitrobiphenyl (CCCLXXVII) shows a number of interesting features that have been rationalized in terms of steric and mesomeric effects[129].



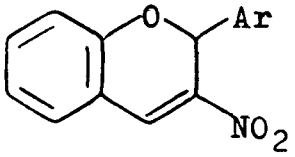
(CCCLXXVII)

A number of β-nitrostyrenes have also been investigated[130] mass spectrometrically and were found to exhibit the characteristics of both aliphatic and aromatic nitro compounds. The mass spectra of β-methyl-β-nitrostyrene (CCCLXXVIII) may be taken as a model compound. It shows a strong molecular ion peak followed by the loss of NO from the molecular ion. This shows that β-nitrostyrenes can rearrange to their isomeric nitrites and it is pertinent to note that photochemical precedent[131] exists for such a reaction.

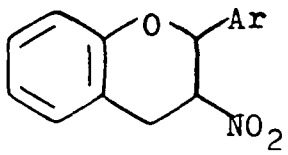


(CCCLXXVIII)

Recently the mass spectra of 3-nitro-2H-chromene (CCCLXXIX) and 3-nitrochroman (CCCLXXX) have been reported[132].

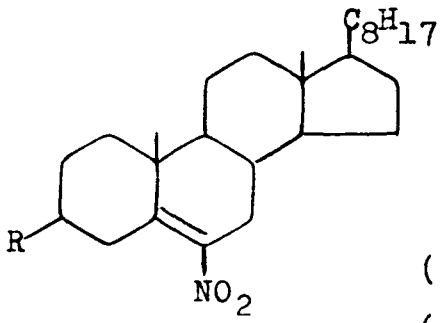


(CCCLXXIX)



(CCCLXXX)

The interesting features of the mass spectra of nitro compounds prompted us to undertake the mass spectral studies of some of the easily accessible steroidal nitroolefins in the cholestane series suchas 6-nitrocholest-5-ene (CCCLXXXI), 3β-chloro-6-nitrocholest-5-ene (CCCLXXXII) and 3β-acetoxy-6-nitrocholest-5-ene (CCCLXXXIII).



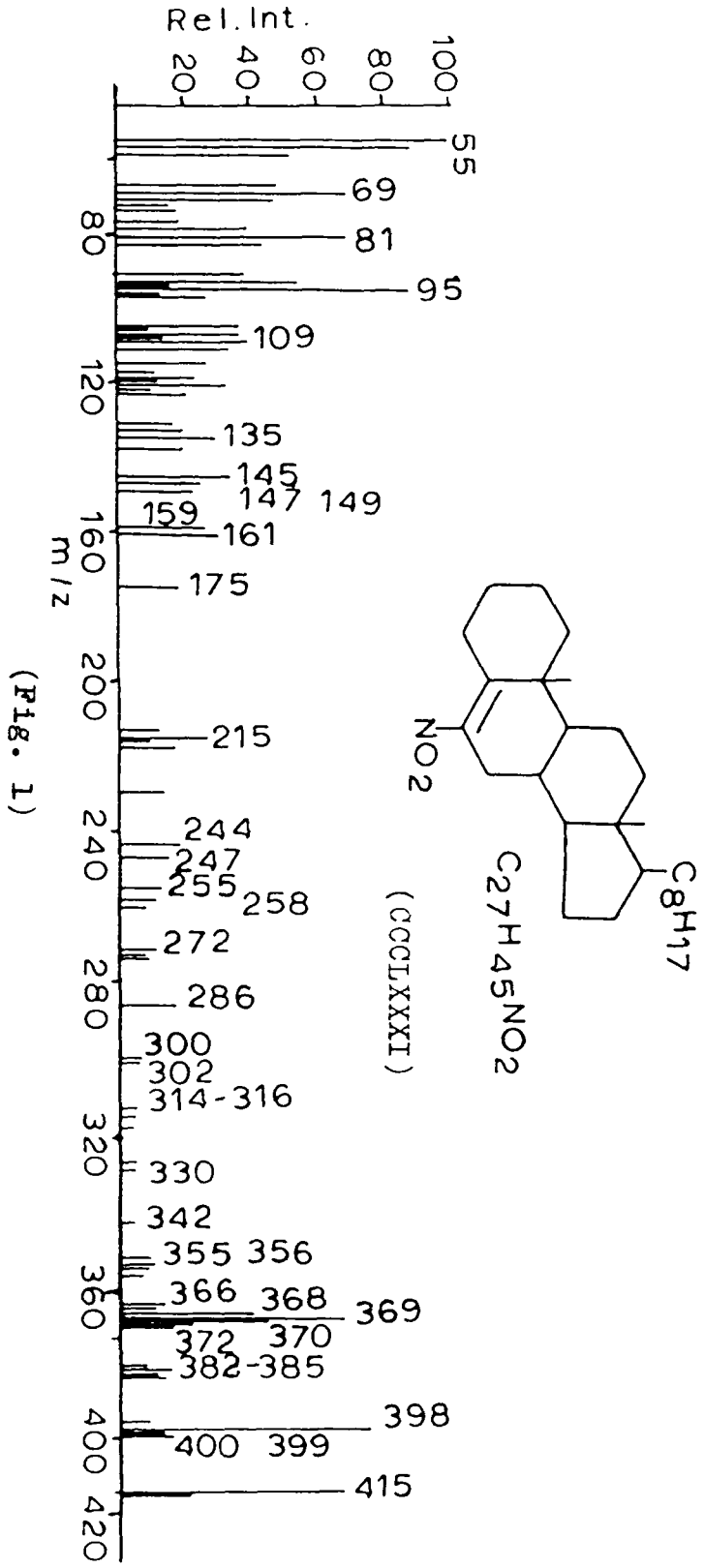
(CCCLXXXI) R, H

(CCCLXXXII) R, Cl

(CCCLXXXIII) R, OAc

The mass spectrum of 6-nitrocholest-5-ene (CCCLXXXI) has been discussed in some detail as this may be considered as the representative model for the nitroolefins. The fragmentation pathways suggested in some cases are supported by appropriate metastable peaks and composition of fragment ions. The mechanistic schemes are tentative in the absence of mass spectra of the appropriate deuterated analogues.

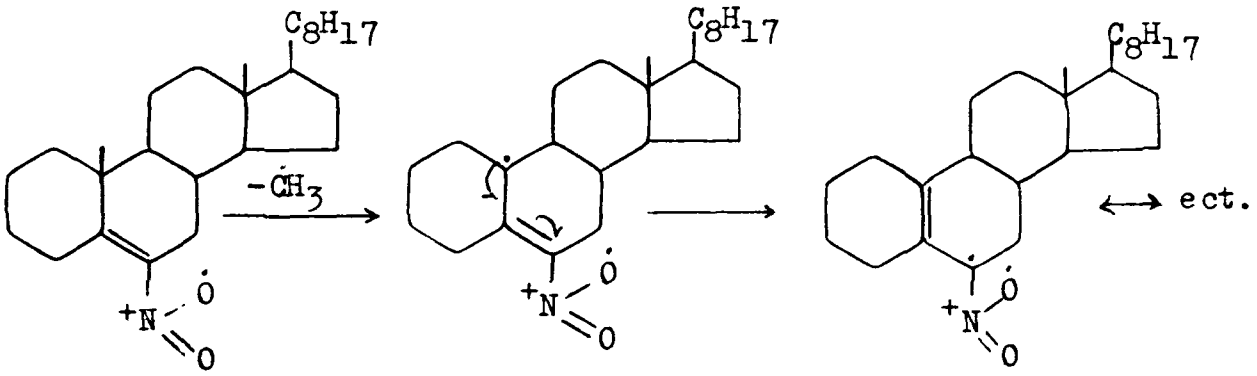
The mass spectrum of 6-nitrocholest-5-ene (CCCLXXXI) (Fig. 1) exhibited the fragment ions which are characteristic of both aliphatic as well as aromatic nitro compounds as does the β-nitrostyrene[130]. The mass spectrum of (CCCLXXXI) showed a relatively strong molecular ion peak at m/z 415 ($C_{27}H_{45}NO_2$) which was reminiscent of aromatic nitro compounds but not of aliphatic nitro compounds, where the molecular ion peaks are either insignificant or are not observed at all[133]. The molecular ion peak was followed by the fragment ion peaks at m/z 400, 399, 398, 385, 384, 383, 382, 372, 371, 370, 369, 368, 367, 366, 358, 356, 355, 354, 353, 342, 330, 328, 316, 314, 302, 300, 286, 272, 258, 255, 247, 244, 232, 230, 218, 216, 215, 213, 175, 161, 159, 149, 147, 145 and lower mass peaks. The genesis of some of the significant fragment ions from (CCCLXXXI) may be explained according to the following schemes.


Rel. Int.
20
40
60
80
100
55
69
81
95
109
135
145
147
149
159
161
175
215
244
247
255
258
272
286
300
302
314-316
330
342
355
356
366
368
369
372
370
382-385
398
400
399
415
m/z
80
120
160
200
240
280
320
360
400
420
NO2
C8H17
C27H45NO2
(CCCLXXXI)

(Fig. 1)

m/z 400

The ion m/z 400, most probably arises by the loss of a methyl radical, preferentially C_{10}-CH_3, from the molecular ion. In this case the species formed is likely to be stabilized. The transition m/z 415 ⟶ m/z 400 is supported by a metastable peak at m/z 385.5 (Calcd. 385.54).

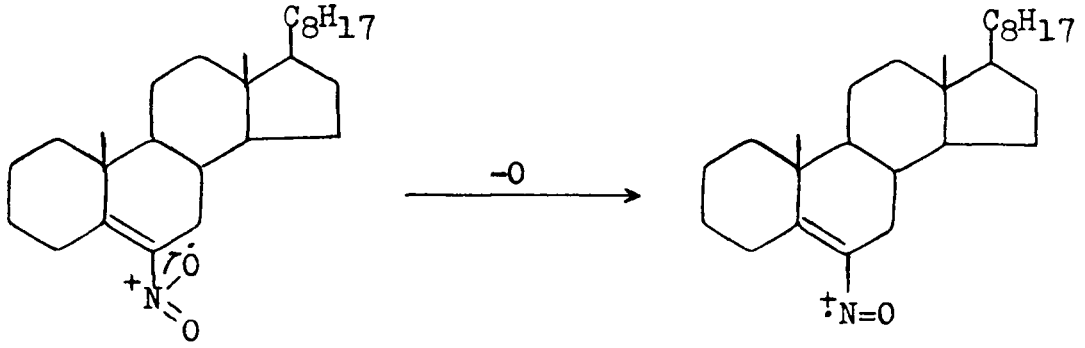


(CCCLXXXI) m/z 400

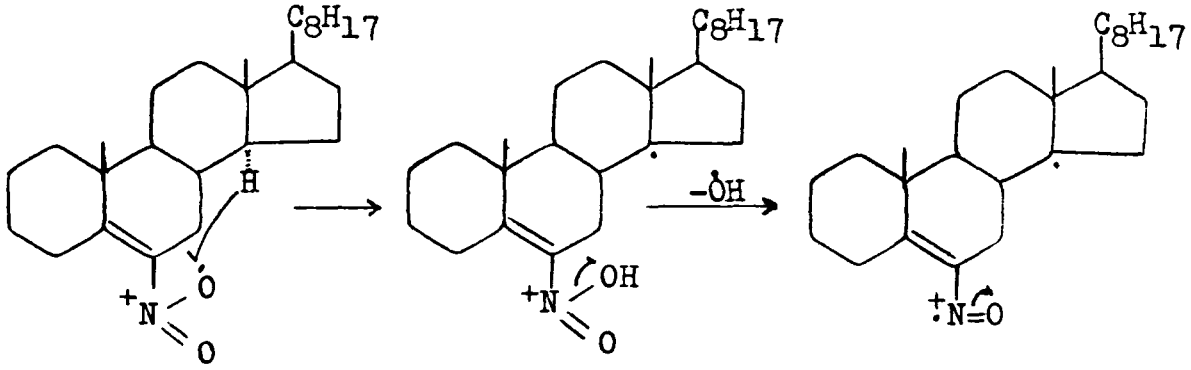
m/z 399 and m/z 398

These ions may arise by the loss of an oxygen atom and a hydroxyl radical, respectively, from the molecular ion. The loss of oxygen and hydroxyl radical constitute one of the most frequently observed fragmentation processes in the mass spectrometry of nitro compounds[133]. The two transitions (m/z 415 ⟶ m/z 399 and m/z 415 ⟶ m/z 398) are supported by metastable peaks observed at 383.6 (Calcd. 383.61) and

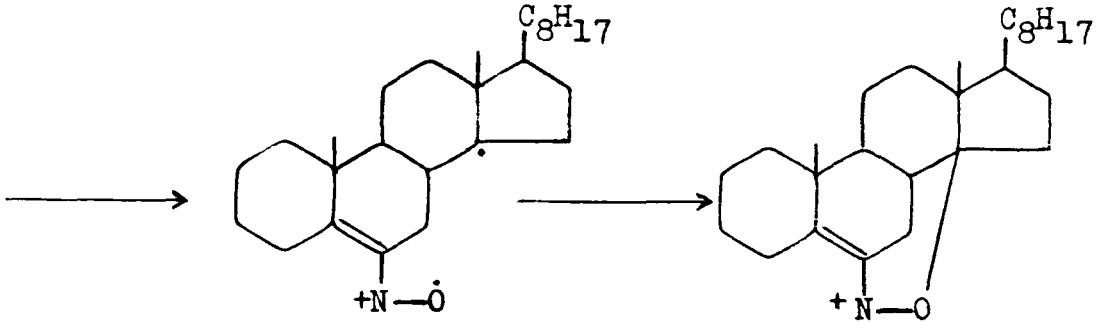
381.7 (Calcd. 381.69), respectively.



(CCCLXXXI) m/z 399(a)

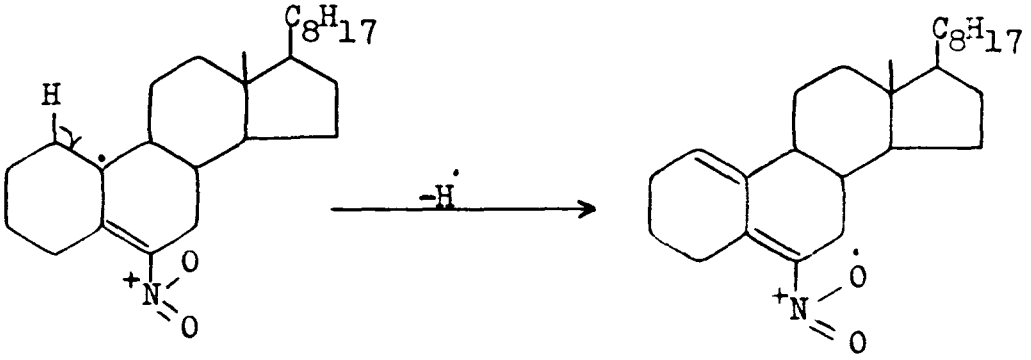


(CCCLXXXI)



m/z 398

Alternatively, the ion m/z 399 can also be shown to arise by the loss of a hydrogen radical from the ion m/z 400. Though no metastable was observed for the transition m/z 400 ⟶ m/z 399, this can not be taken as an evidence against this transition.

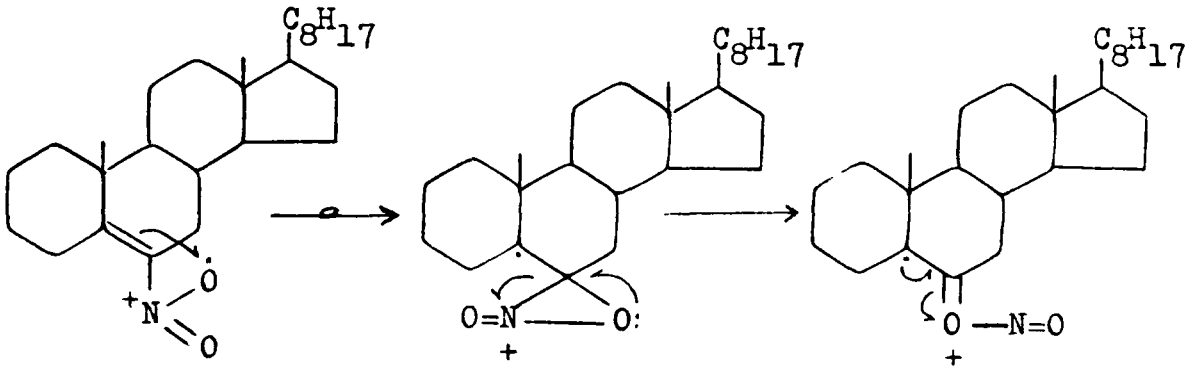


m/z 400 m/z 399(b)

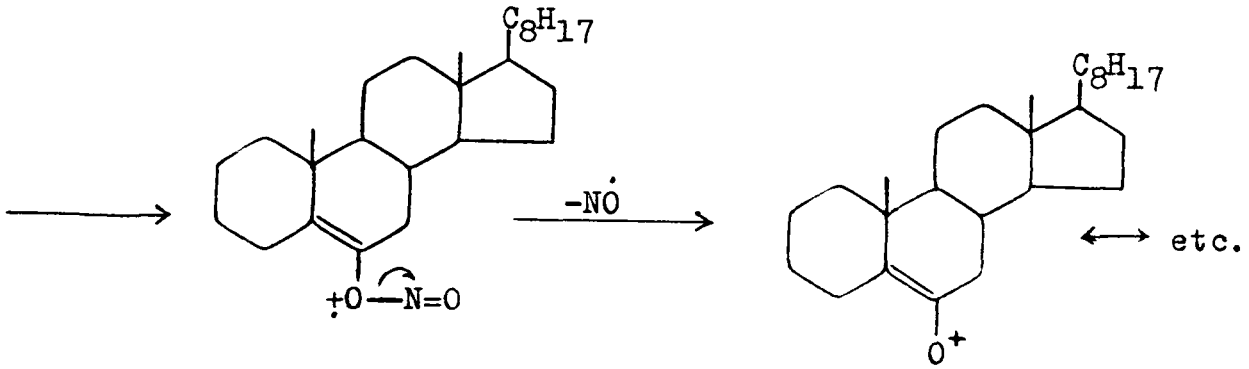
m/z 385

The fragment ion m/z 385 is most likely formed by the loss of nitric oxide (NO) from the molecular ion. Though the loss of NO from the molecular ion is characteristic of aromatic nitro compounds but the evidence for such a loss from nitroolefins also exists[130]. The loss of nitric oxide from a nitro group has been explained on the basis of its rearrangement to the isomeric nitrite form prior to the fragmentation in a one-step process. It is pertinent to note that the photochemical precedent[131] exists for such a rea-

rrangement. The transition m/z 415 ⟶ m/z 385 finds support by metastable ion at m/z 357.2 (Calcd. 357.16).



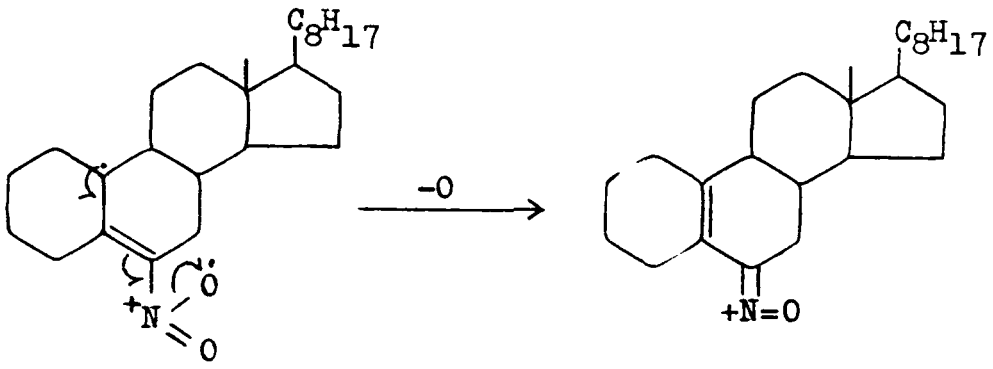
(CCCLXXXI)



m/z 385

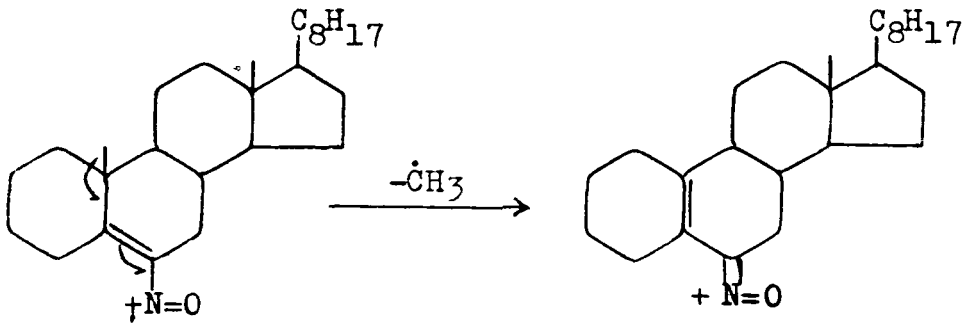
m/z 384

The ion m/z 384 may be shown to arise by the loss of an oxygen atom from the ion m/z 400. Inversely, this ion may also arise by the loss of a methyl radical from the ion m/z 399, formed by the loss of an oxygen atom from the molecular ion.



m/z 400 m/z 384

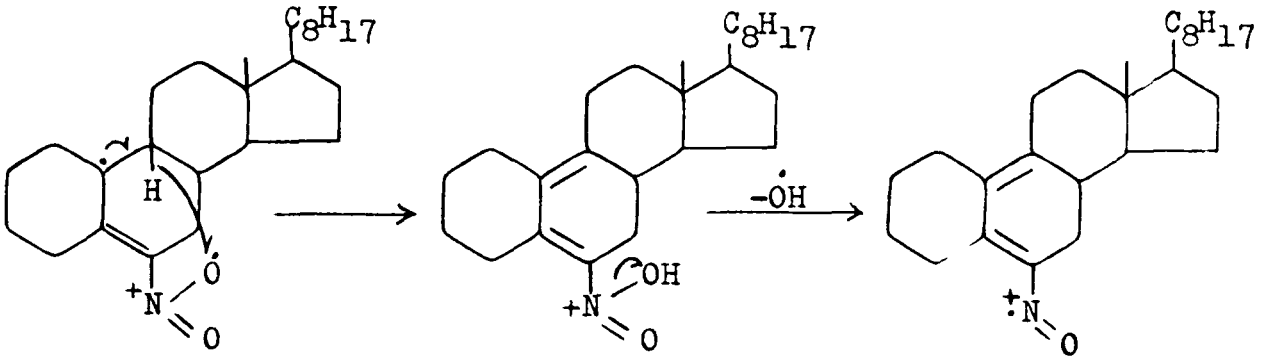
OR



m/z 399 m/z 384

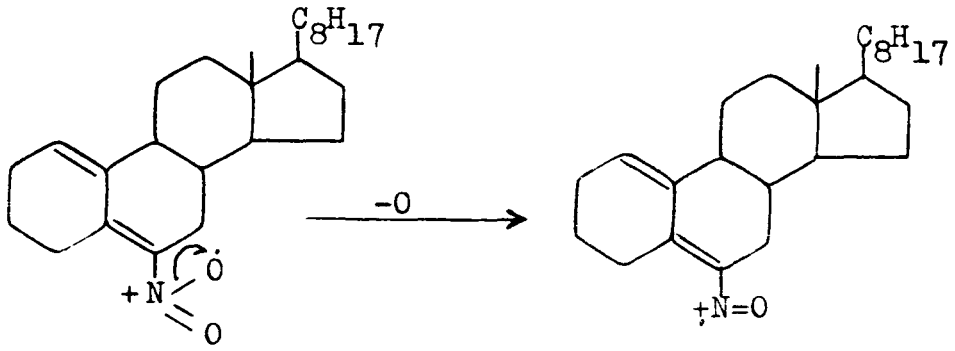
m/z 383

This ion most probably arises by the loss of a hydroxyl radical from the ion m/z 400.



m/z 400 m/z 383

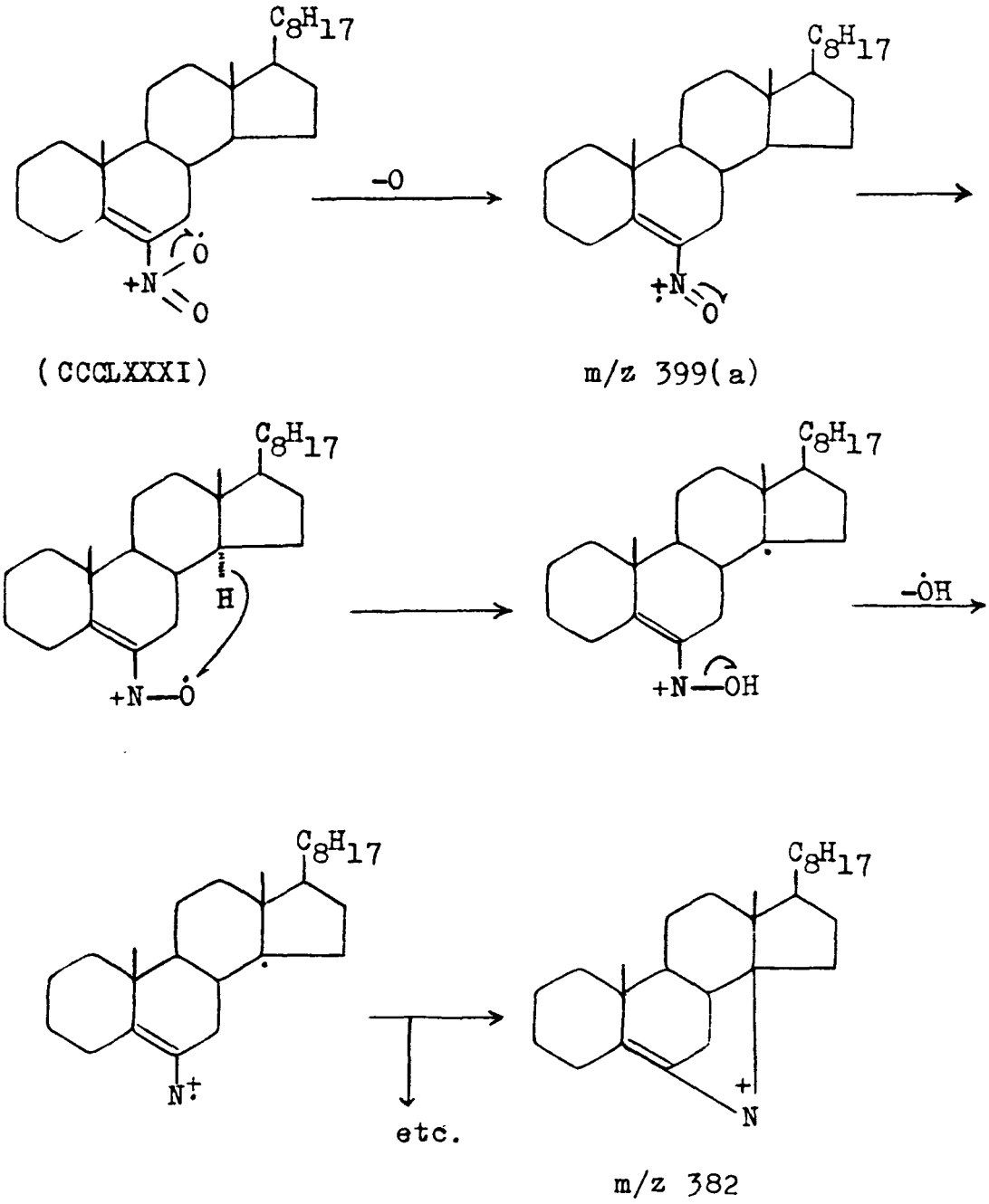
Alternatively, the ion m/z 383 may also arise by the loss of an oxygen atom from the ion m/z 399 (b).



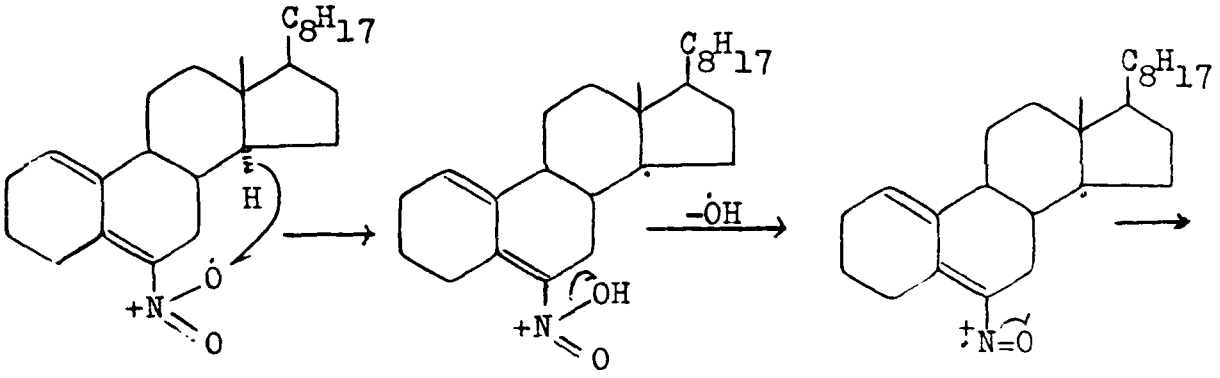
m/z 399(b) m/z 383

m/z 382

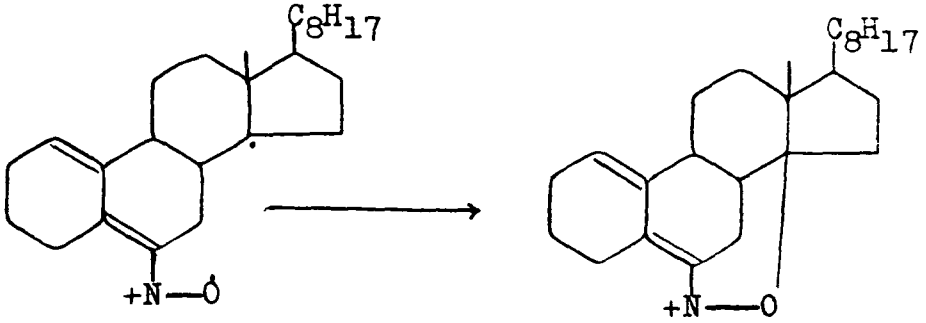
The ion m/z 382 may be shown to arise by the loss of both the oxygen atoms, apparently by the sequential elimination of an oxygen and of a hydroxyl radical.



Alternatively, this ion can also arise from the ion m/z 399 (b) by the loss of a hydroxyl radical.



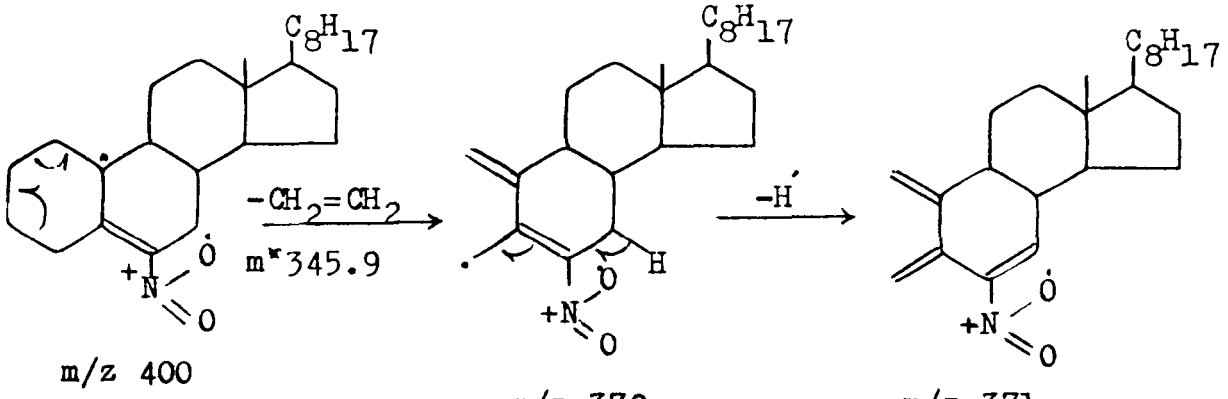
m/z 399(b)



m/z 382

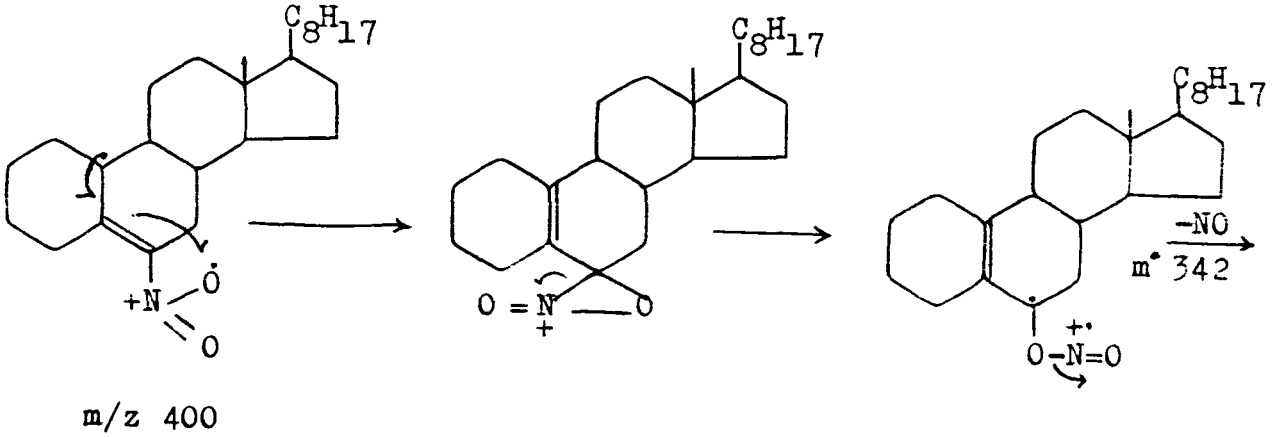
<u>m/z 372 and m/z 371</u>

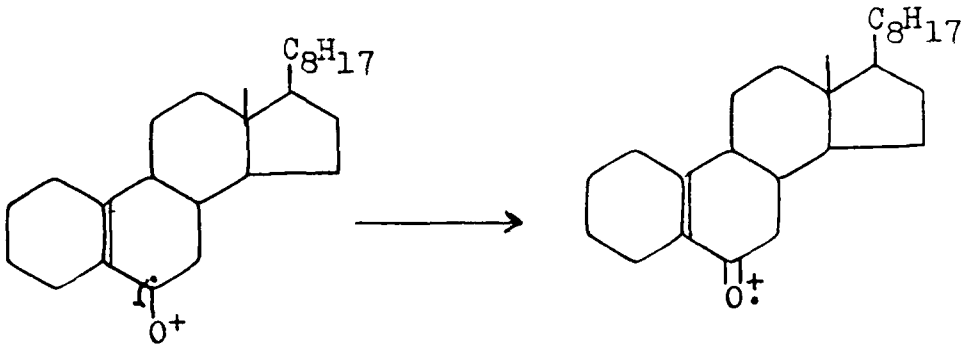
The ion m/z 372 arises from the ion m/z 400, by the loss of ethylene from ring A. Further loss of hydrogen from the ion m/z 372 gives the ion m/z 371.



m/z 370

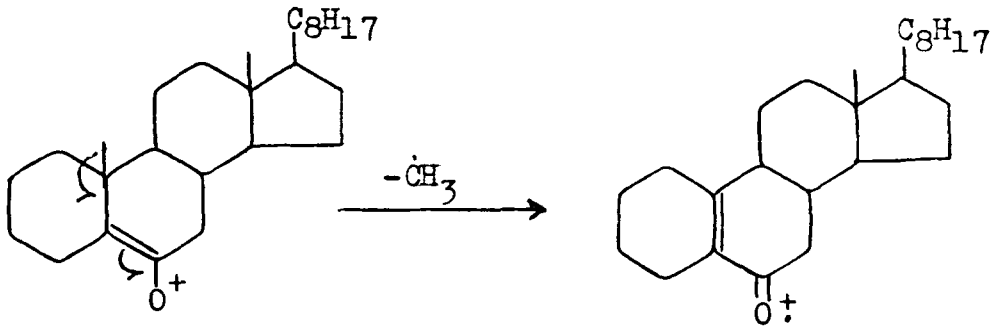
This ion may be accounted for by the loss of nitric oxide from the ion m/z 400. The ion m/z 400, undergoes rearrangement to the isomeric nitrite form which then eliminates nitric oxide to give the ion m/z 370.





m/z 370

Alternatively, this ion can also arise from the ion m/z 385 by the loss of a methyl radical.

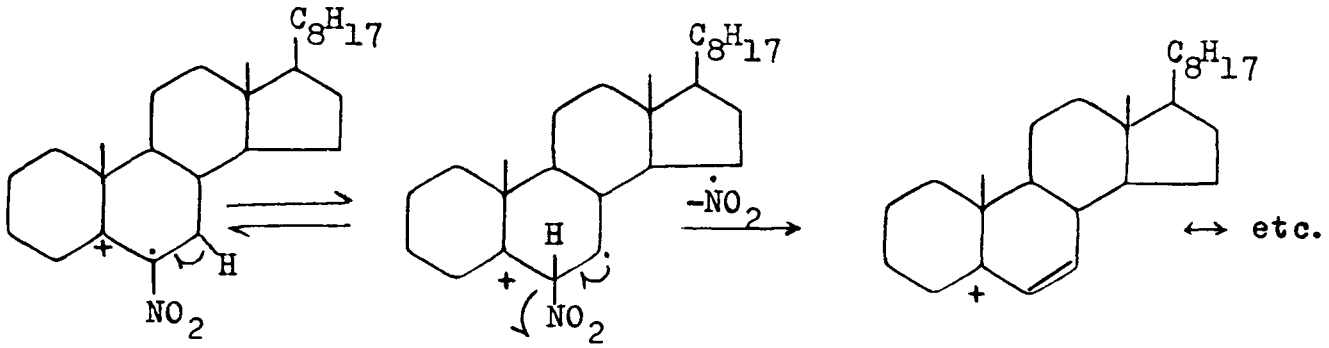


m/z 385 m/z 370

<u>m/z 369 and m/z 368</u>

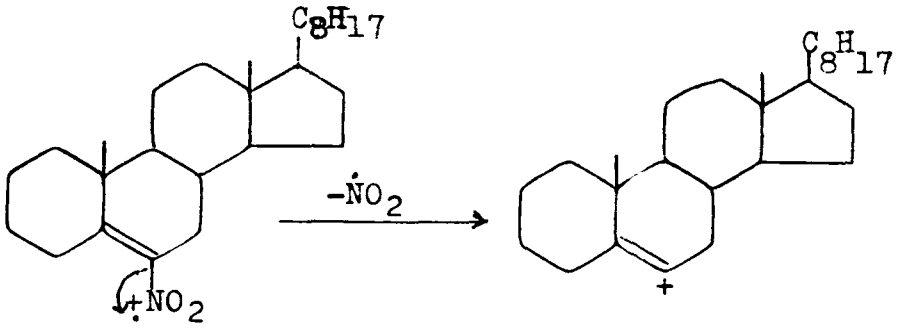
The ion m/z 369, constituting the base peak in the mass spectrum of (CCCLXXXI) most probably arises by the loss

of NO_2 from the molecular ion. The loss of NO_2 from the molecular ion is one of the most significant fragmentations[133] in the mass spectra of aliphatic and alicyclic nitro compounds and is responsible for the base peak in most of the cases. The ion m/z 368 may arise by the loss of the elements of nitrous acid[119] from the molecular ion. The loss of NO_2 from the molecular ion, by analogy, can be written as in the following scheme.



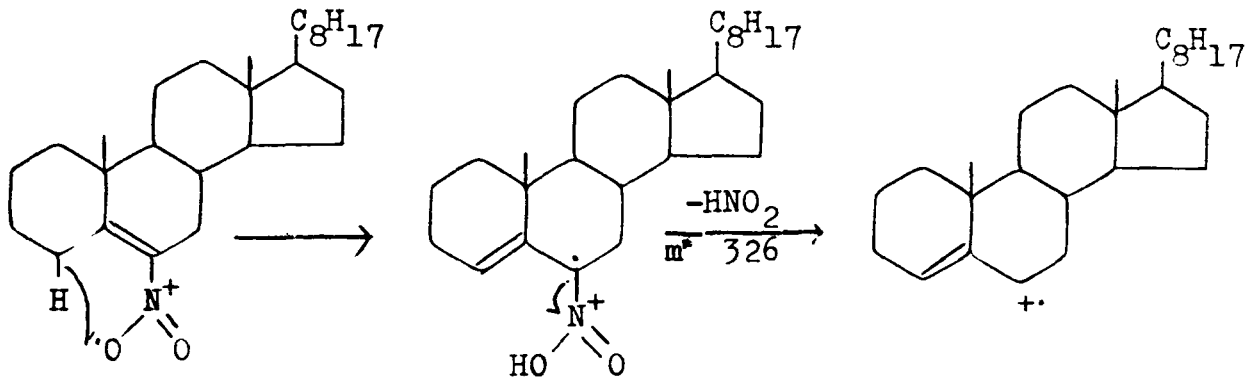
m/z 415 m/z 369($C_{27}H_{45}$)

OR



(CCCLXXXI) m/z 369

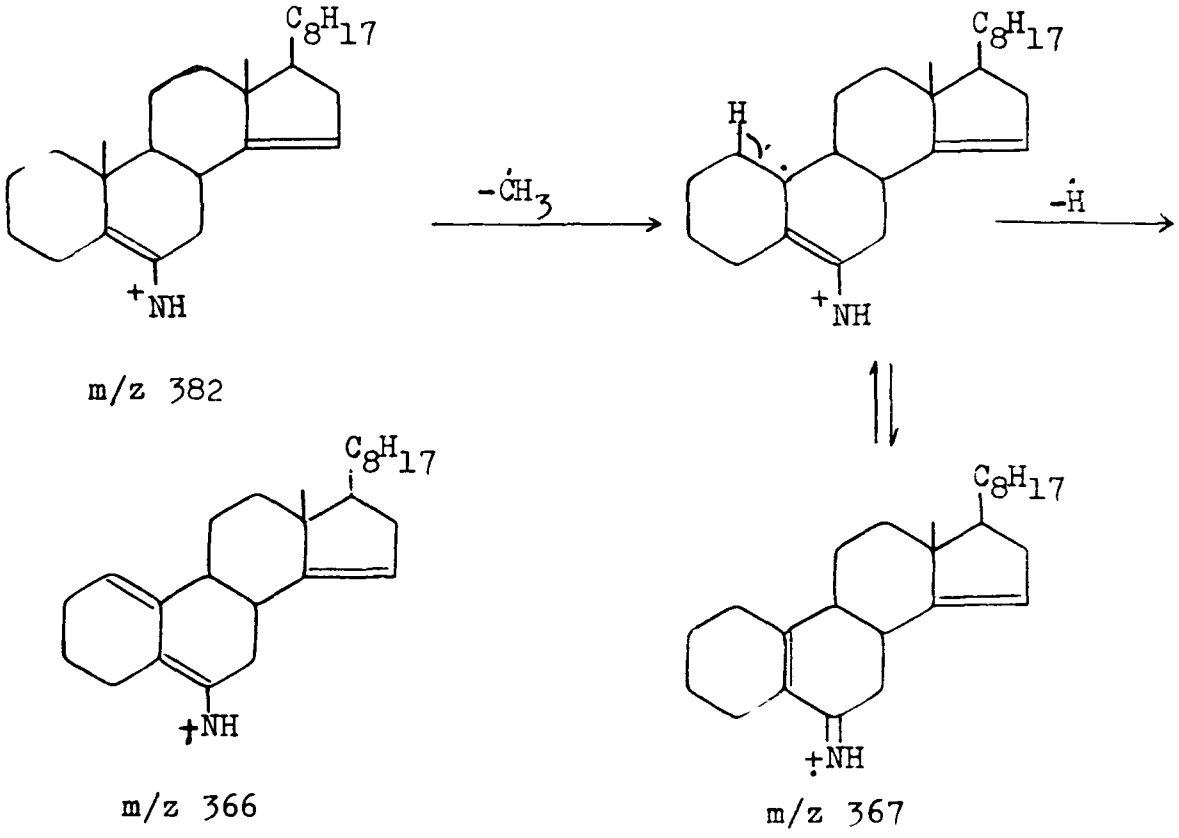
The transition m/z 415 ⟶ m/z 369 finds support from a metastable peak at m/z 328.2 (Calcd. 328.09). There could be other precursor for the ion m/z 369, for example m/z 370 - H. The ion m/z 368 arises from the molecular ion as follows.



(CCCLXXXI) m/z 368($C_{27}H_{44}$)

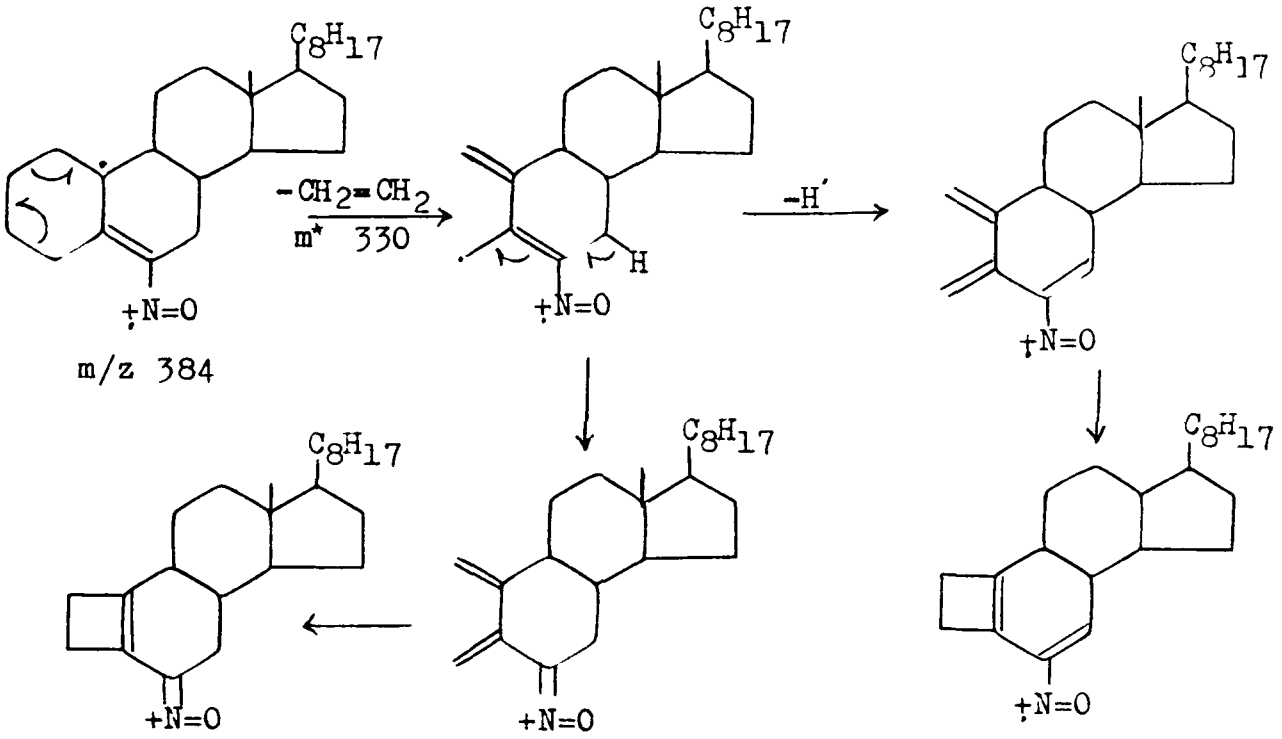
m/z 367 and m/z 366

The ion m/z 367 may be shown to arise by the loss of a methyl radical from the ion m/z 383; subsequent loss of a hydrogen may give the ion m/z 366.

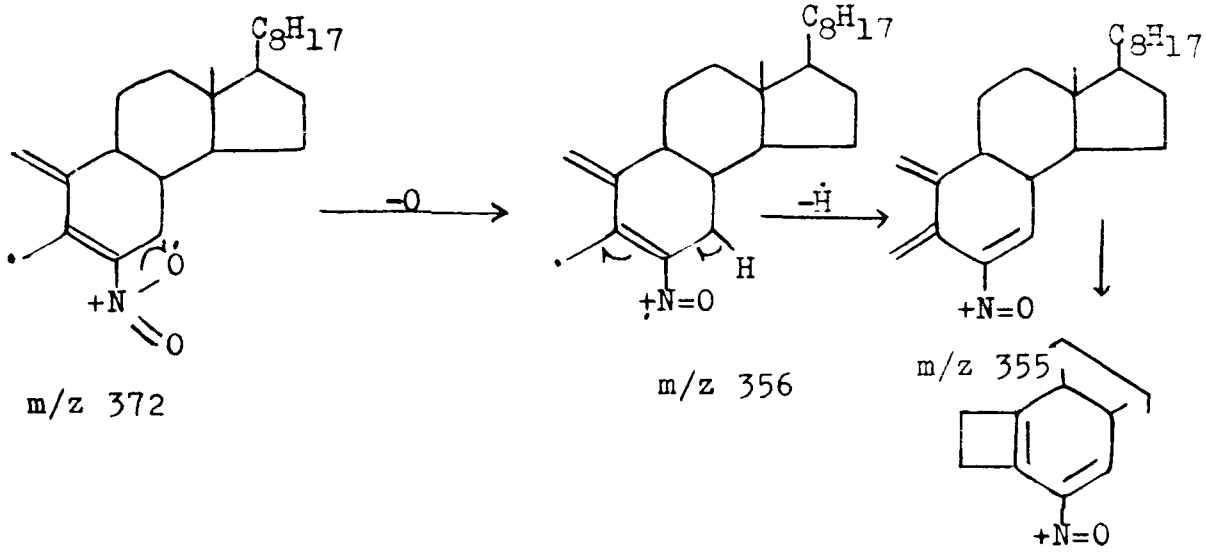


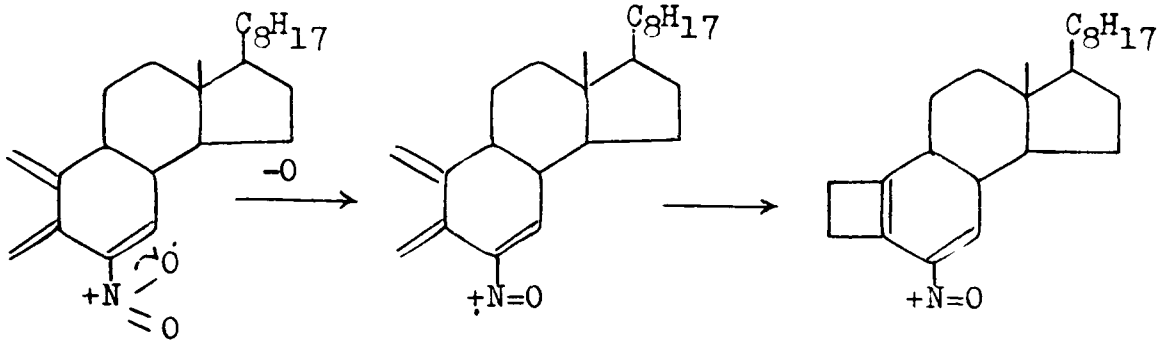
m/z 356 and m/z 355

The ion m/z 356 arises most probably from the ion m/z 384 by the loss of ethylene. The ion m/z 356 may then lose a hydrogen radical to give the ion m/z 355.



Alternatively, these ions may also arise by the loss of an oxygen atom from the ions m/z 372 and 371, respectively.

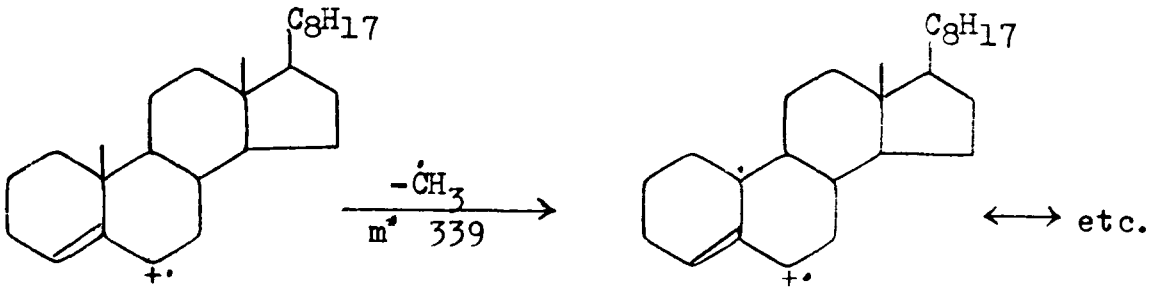




m/z 371 m/z 355

m/z 353

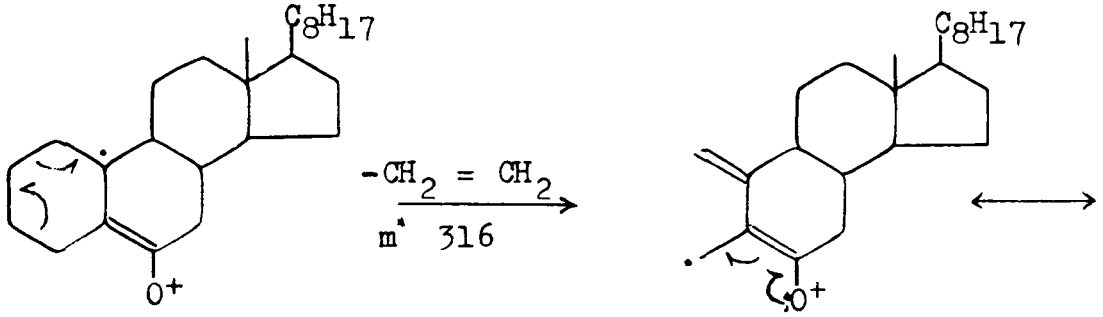
This ion arises most probably by the loss of a methyl radical from the ion m/z 368.



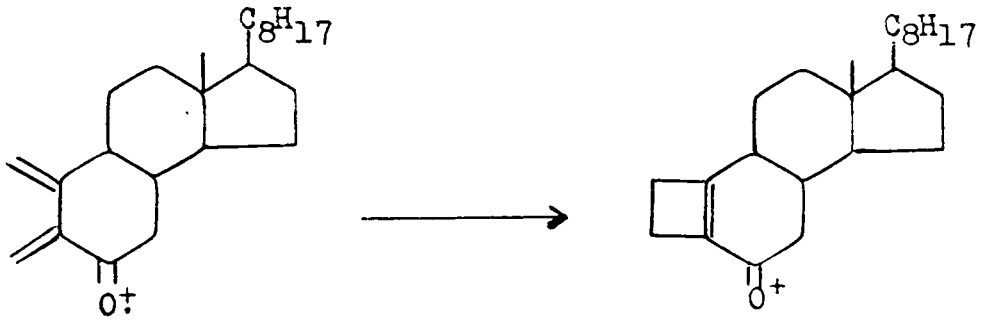
m/z 368($C_{27}H_{44}$) m/z 353

m/z 342

The ion m/z 342 may be shown to arise by the loss of ethylene from the ion m/z 370.



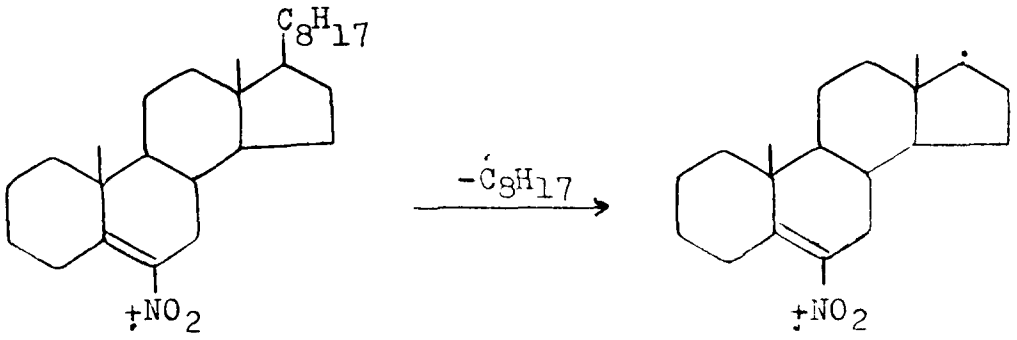
m/z 370



m/z 342

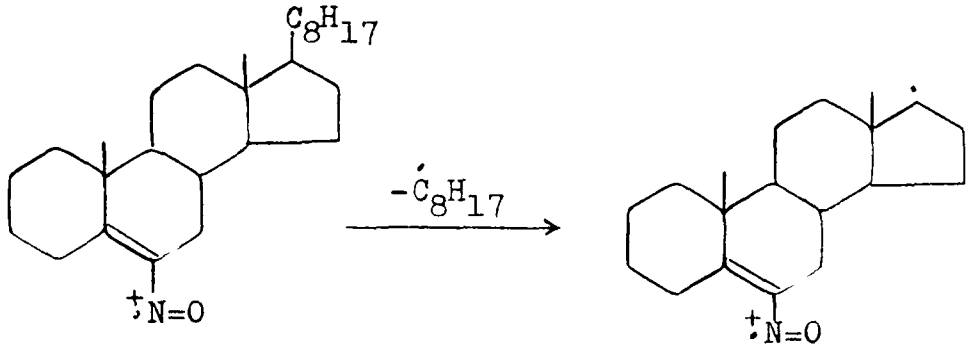
<u>m/z 302, m/z 286 and m/z 272</u>

These ions may be shown to arise by the loss of the side chain (C_8H_{17}) from the molecular ion, m/z 399 and m/z 385, respectively. The loss of the side chain on electron-impact is a common phenomenon in the mass spectrometry of steroidal compounds.



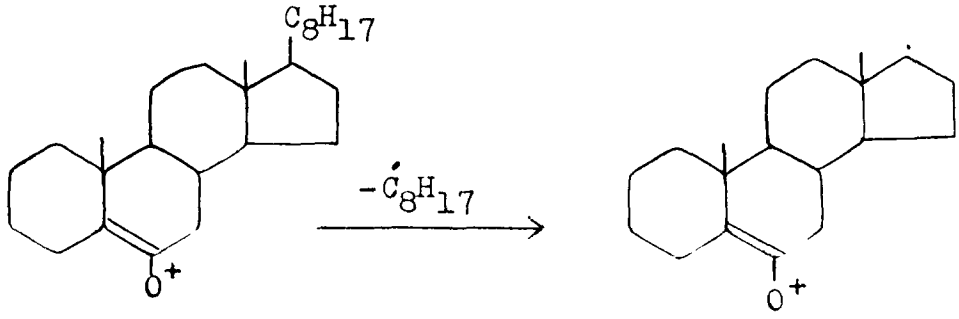
(CCCLXXXI)

m/z 302



m/z 399

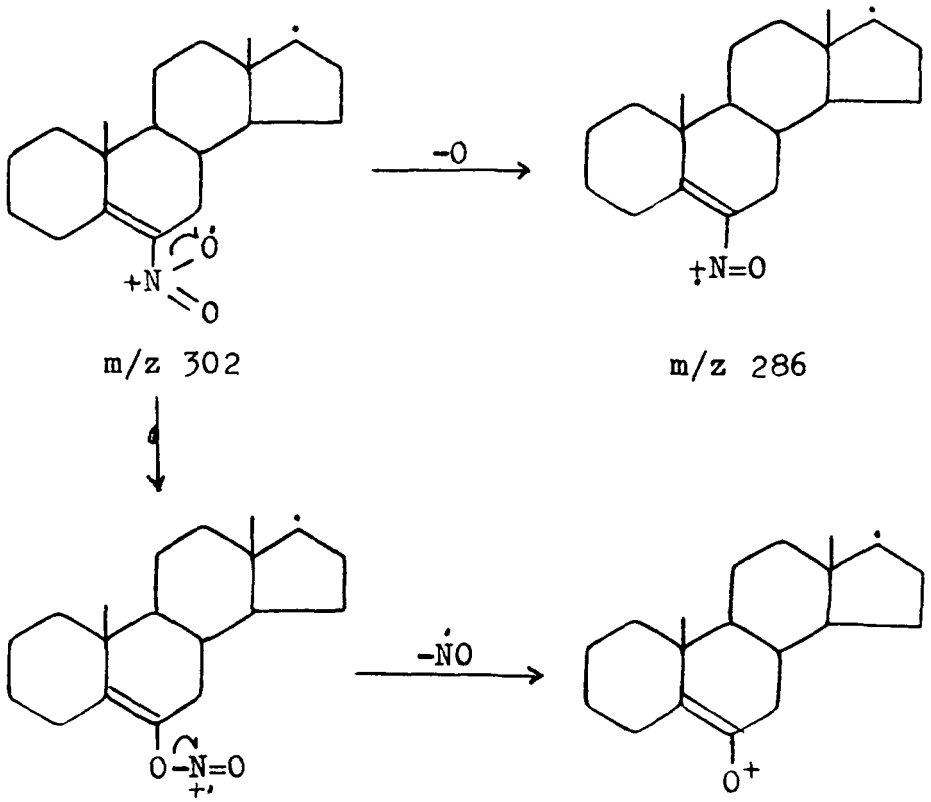
m/z 286



m/z 385

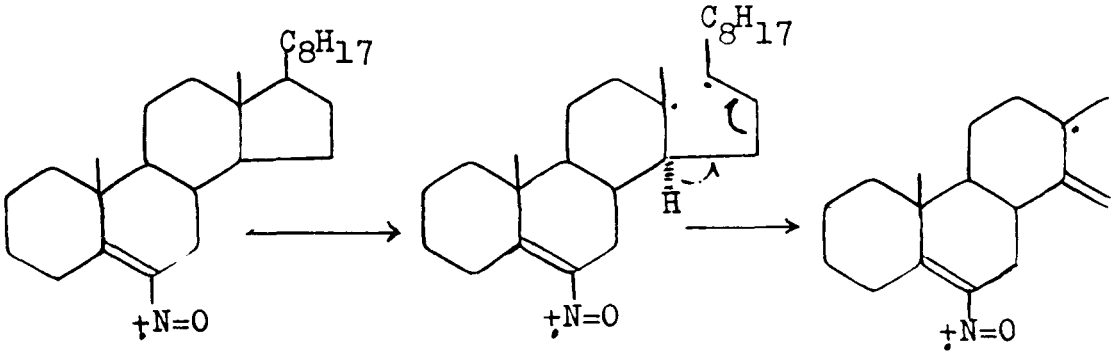
m/z 272

Alternatively, the ions m/z 286 and m/z 272 may also be shown to arise by the loss of oxygen and nitric oxide respectively from the ion m/z 302.



m/z 258

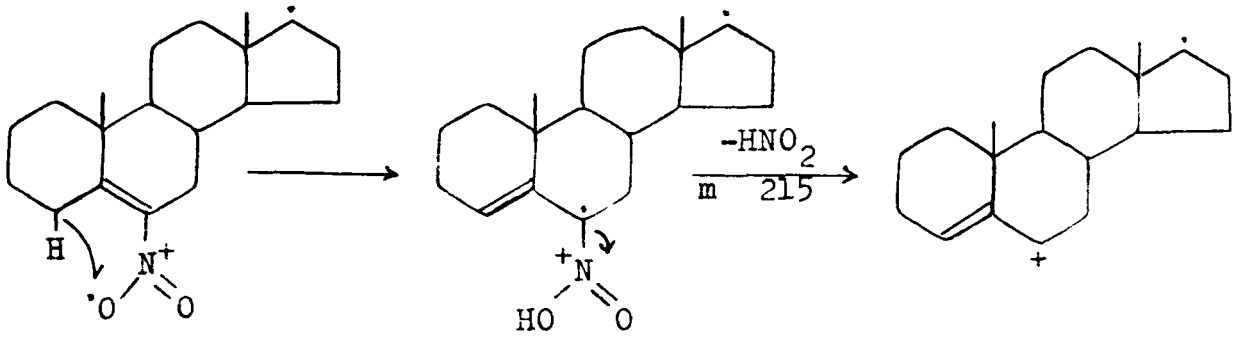
This ion may be shown to arise from the ion m/z 399 by the loss of the side chain along with part of the ring D.



m/z 399 m/z 258

m/z 255

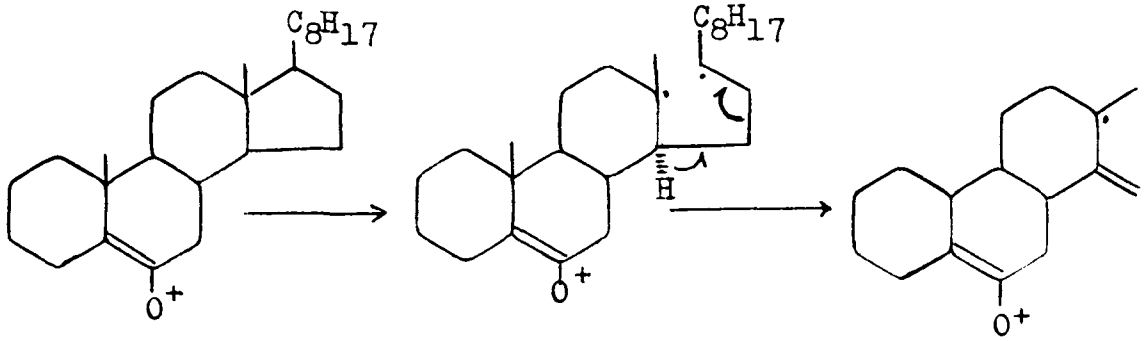
This ion most probably arises by the loss of the elements of nitrous acid from the ion m/z 302.



m/z 302 m/z 255($C_{19}H_{27}$)

m/z 244

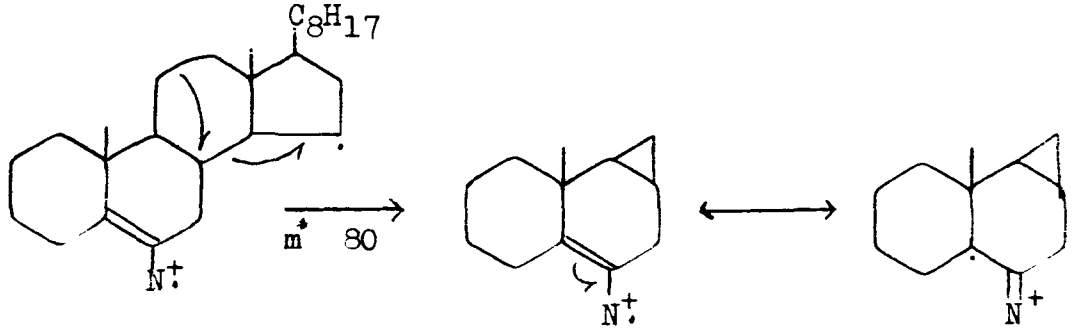
The ion m/z 244 may be formed by the loss of the side chain along with a part of the ring D from the ion m/z 385.



m/z 385 m/z 244

m/z 175 ($C_{12}H_{17}N$)

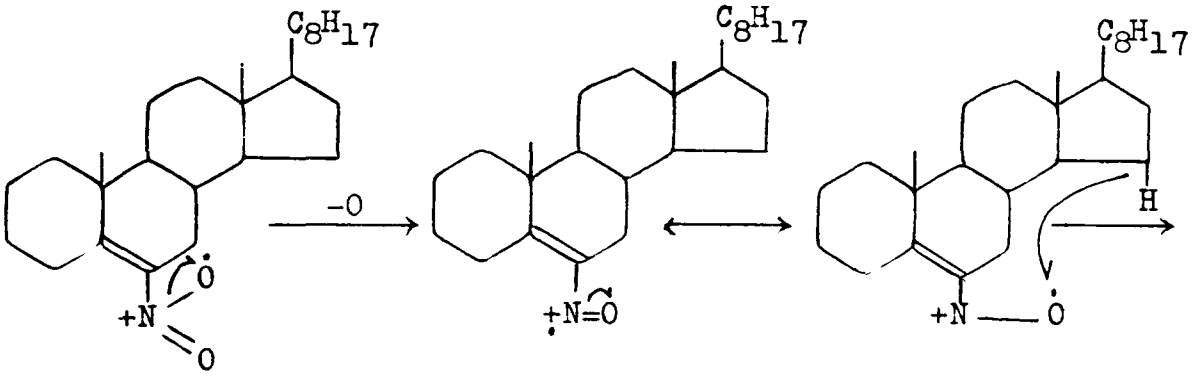
This ion is most probably obtained by the loss of side chain along with ring D and part of ring C from the ion m/z 382.



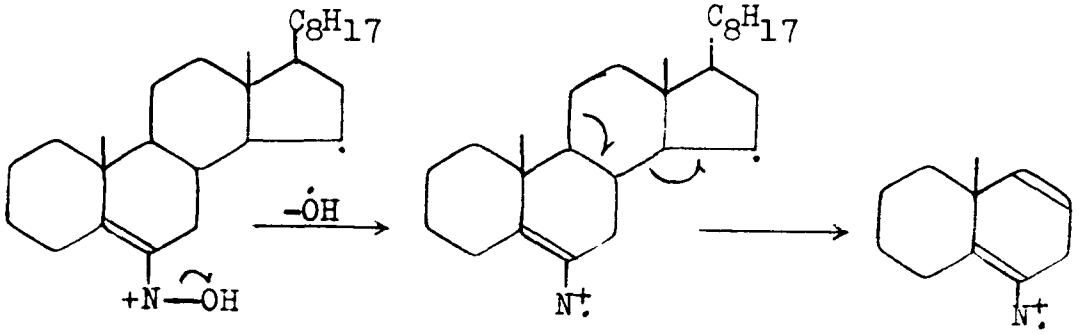
m/z 382 m/z 175($C_{12}H_{17}N$)

m/z 161 ($C_{11}H_{15}N$)

The ion m/z 161 can be shown to arise by the loss of rings C and D along with the side chain and the two oxygen atoms of the nitro group. The probable pathway involved in the formation of this ion can be shown as follows:



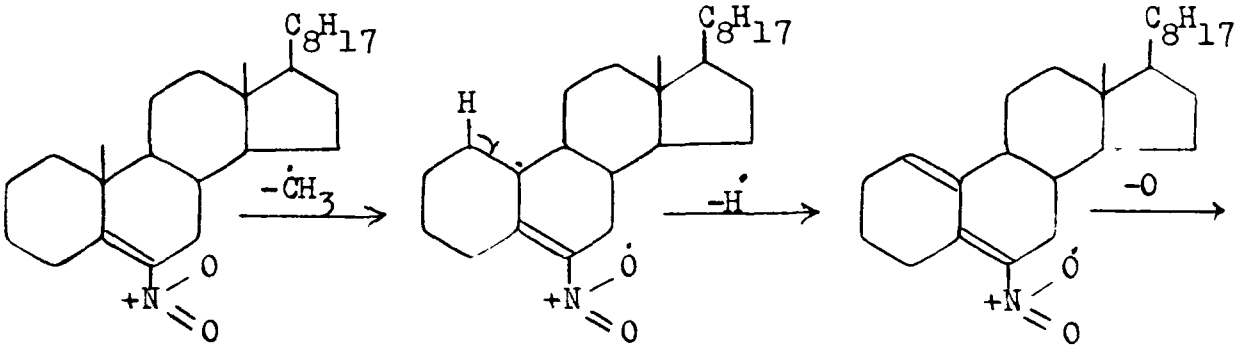
(CCCLXXXI) m/z 399



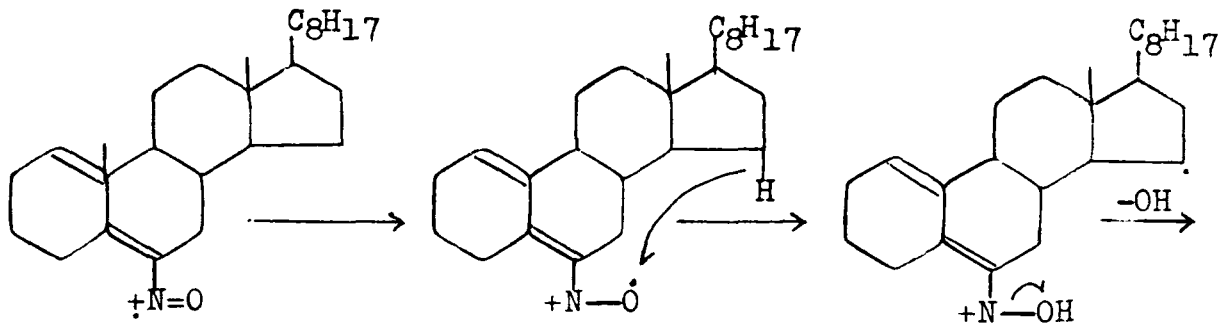
m/z 161($C_{11}H_{15}N$)

m/z 159 ($C_{11}H_{13}N$)

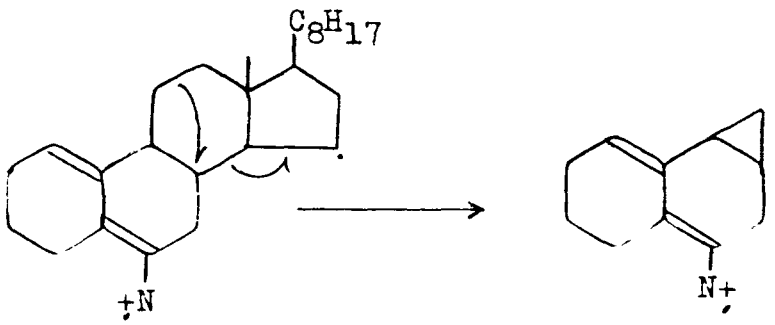
The ion m/z 159 ($C_{11}H_{13}N$) can be shown to arise by the following pathway.



(CCCLXXXI) m/z 400 m/z 399



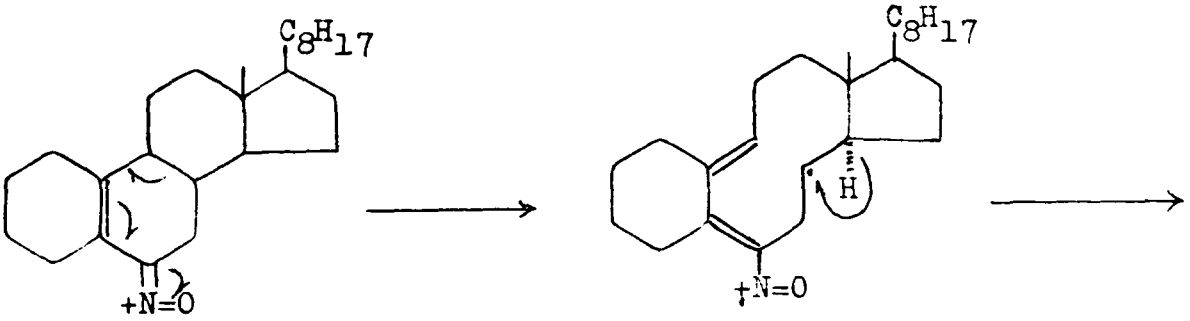
m/z 383



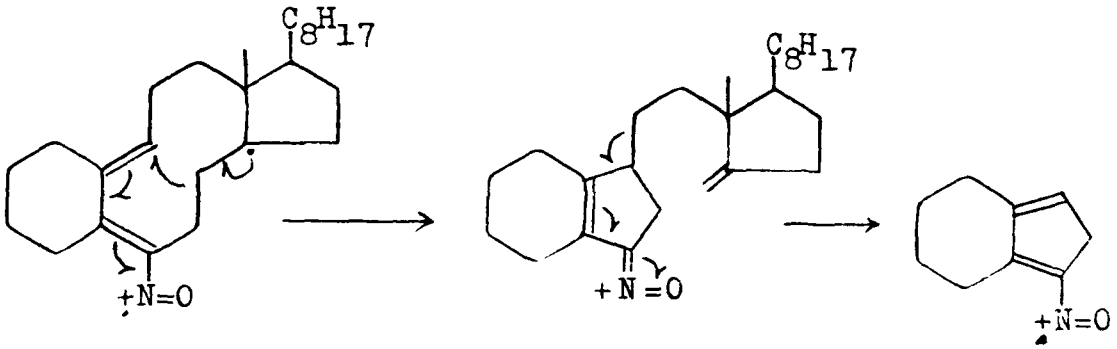
m/z 366 m/z 159($C_{11}H_{13}N$)

m/z 149 ($C_9H_{11}NO$)

The ion m/z 149 may be formed by the following sequence.



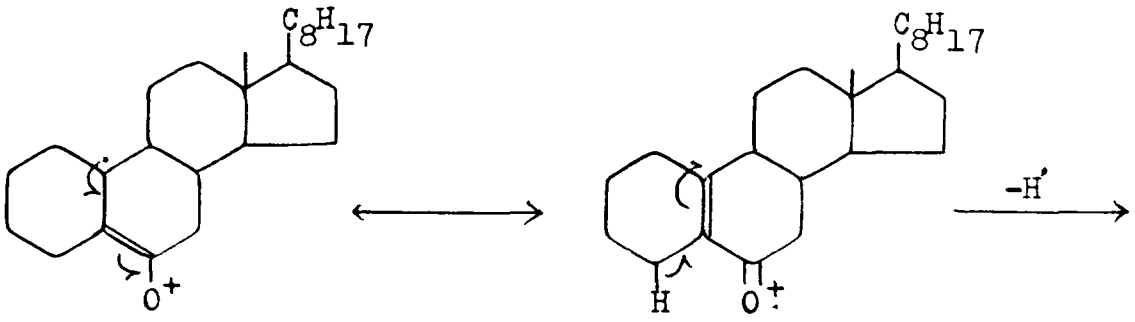
m/z 384



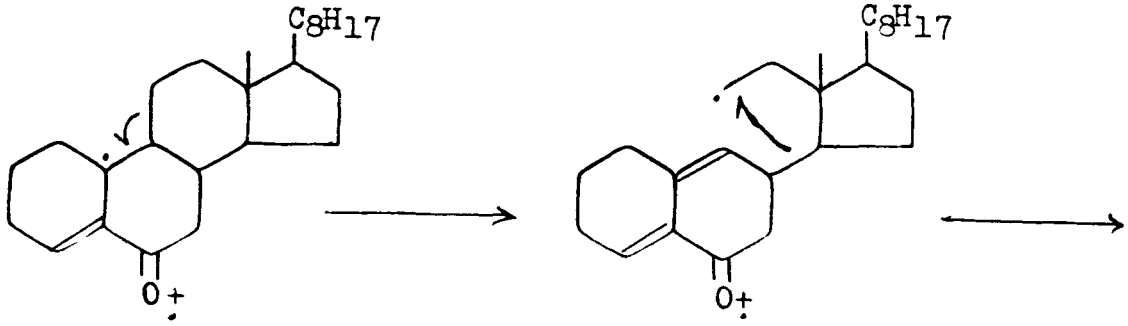
m/z 149($C_9H_{11}NO$)

m/z 147 ($C_{10}H_{11}O$)

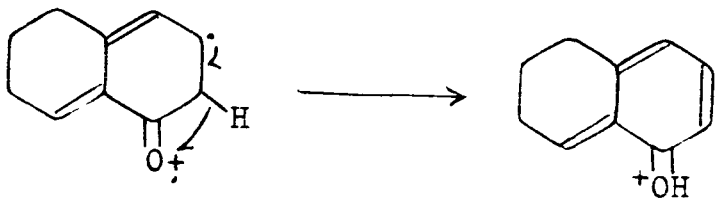
The ion m/z 147 may be shown to arise according to the following scheme.



m/z 370



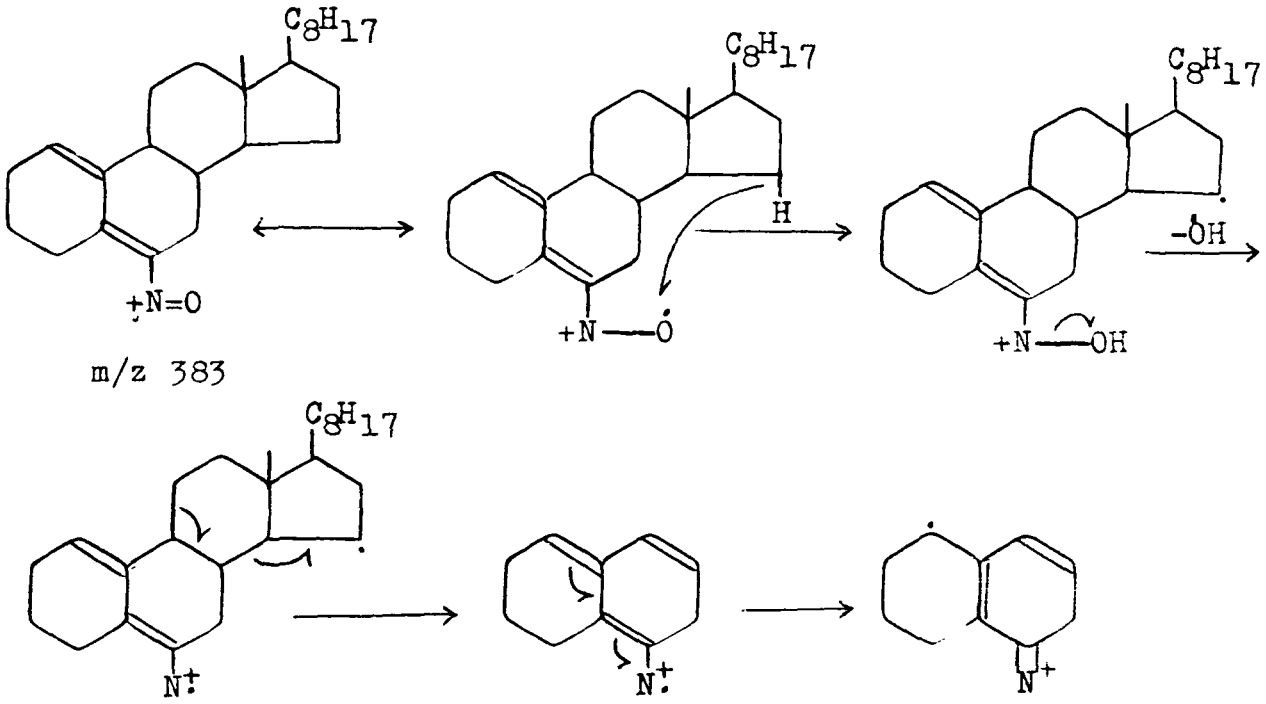
m/z 369



m/z 147($C_{10}H_{11}O$)

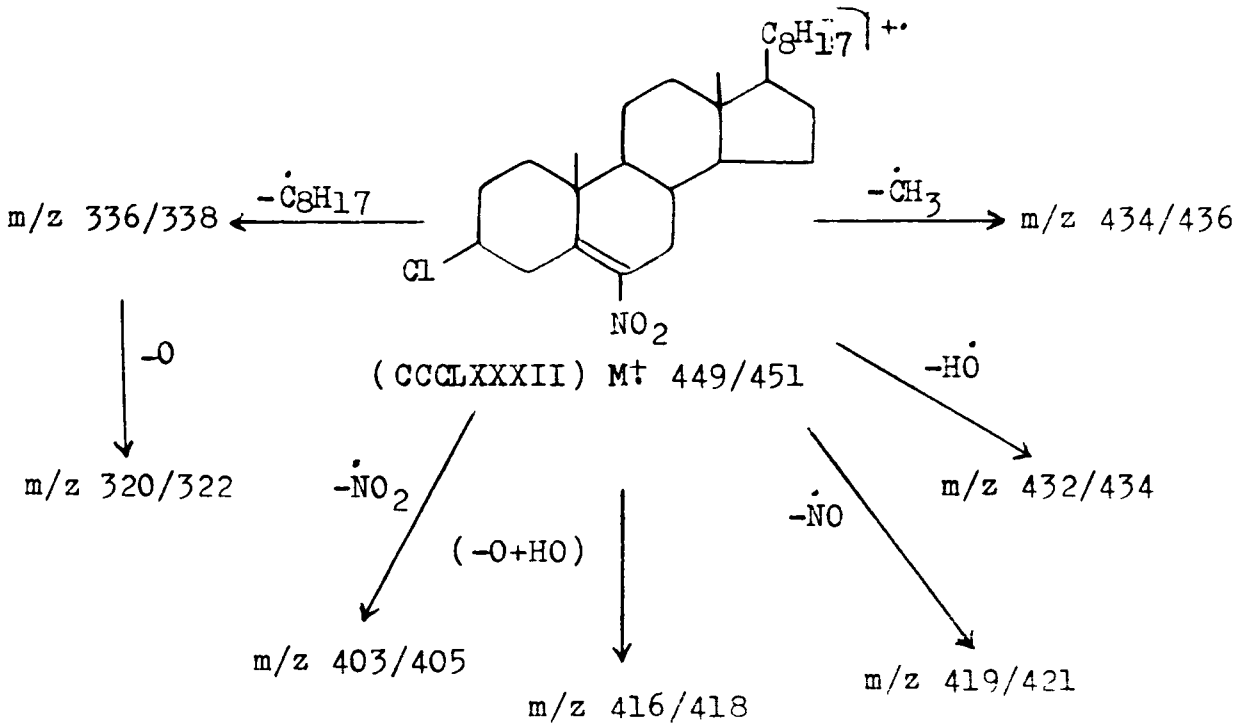
m/z 145 ($C_{10}H_{11}N$)

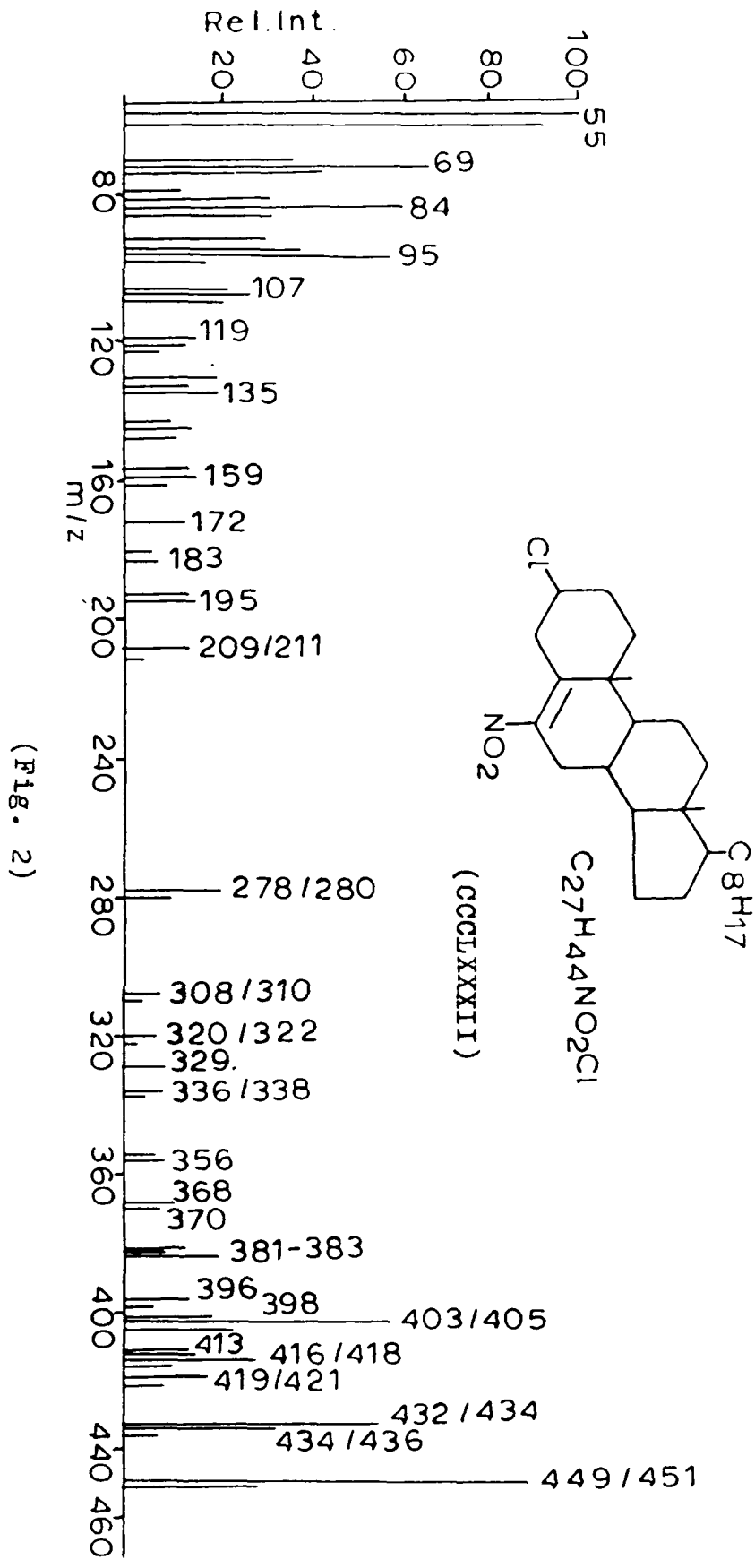
The ion m/z 145 ($C_{10}H_{11}N$) arises most probably by the fragmentation process shown below.



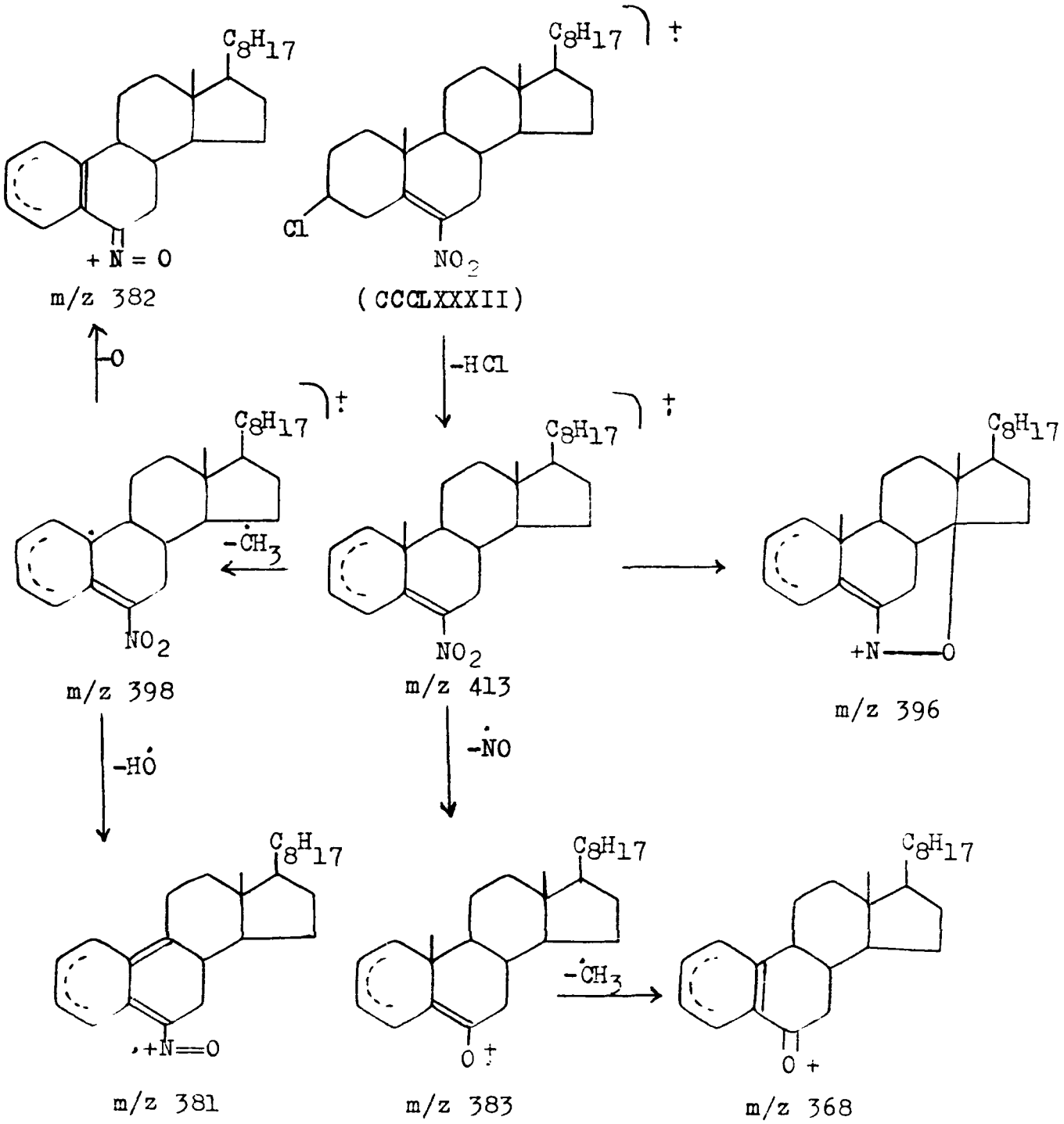
The mass spectra of 3β-chloro-6-nitrocholest-5-ene (CCCLXXXII) and 3β-acetocy-6-nitrocholest-5-ene (CCCLXXXIII) were comparable with that of the 6-nitrocholest-5-ene (CCCLXXXI).

The mass spectrum of (CCCLXXXII) (Fig. 2) gave the molecular ion peak at m/z 449/451. Most of the fragment ions were formed after the loss of HCl from the molecular ion[134]. Some chlorine containing ions were also recroded which were of special significance as they served as a lable due to the isotopic nature of chlorine and helped to a great extent in the interpretation of the spectra. The genesis of some of the ions has been shown in the following schemes.

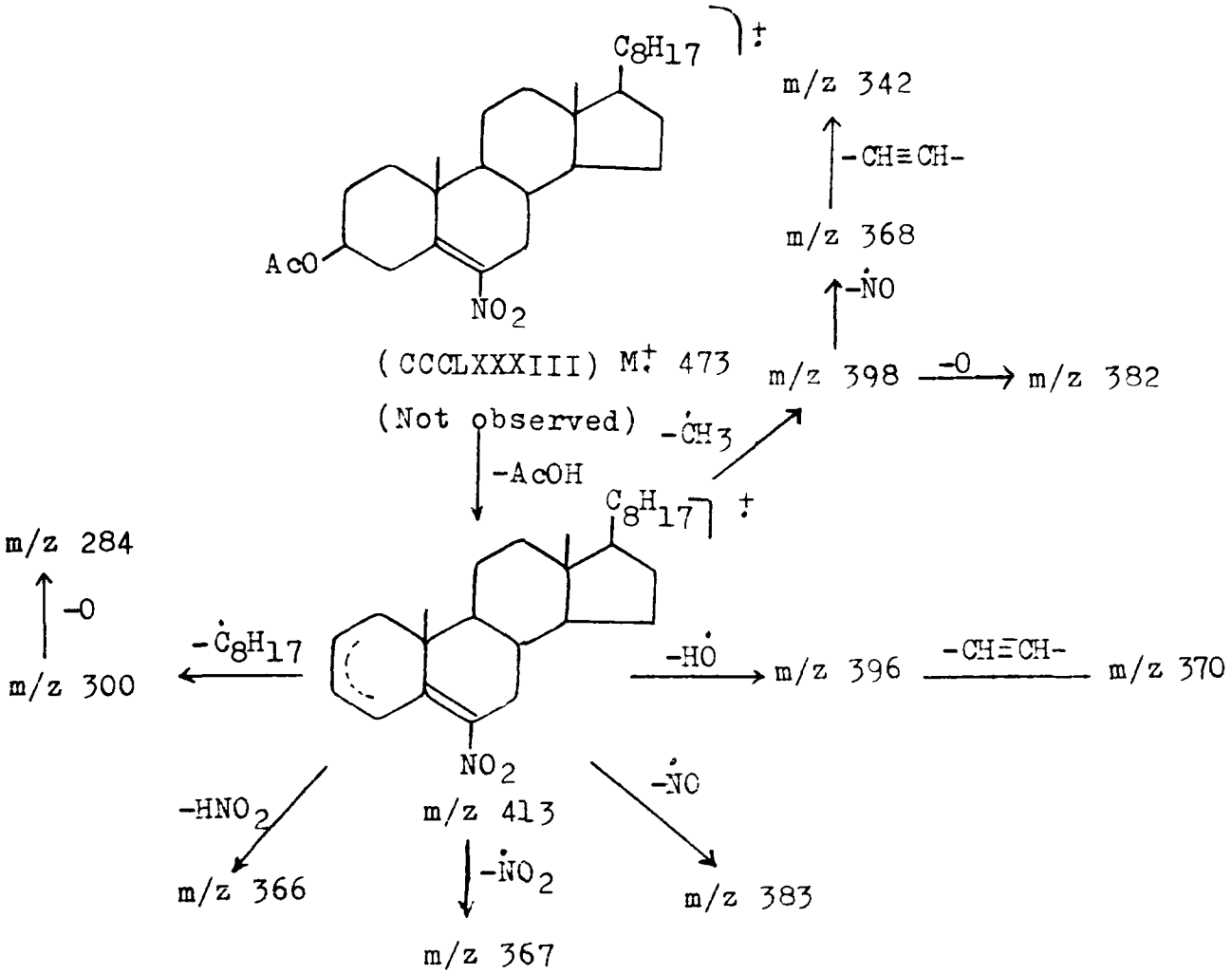


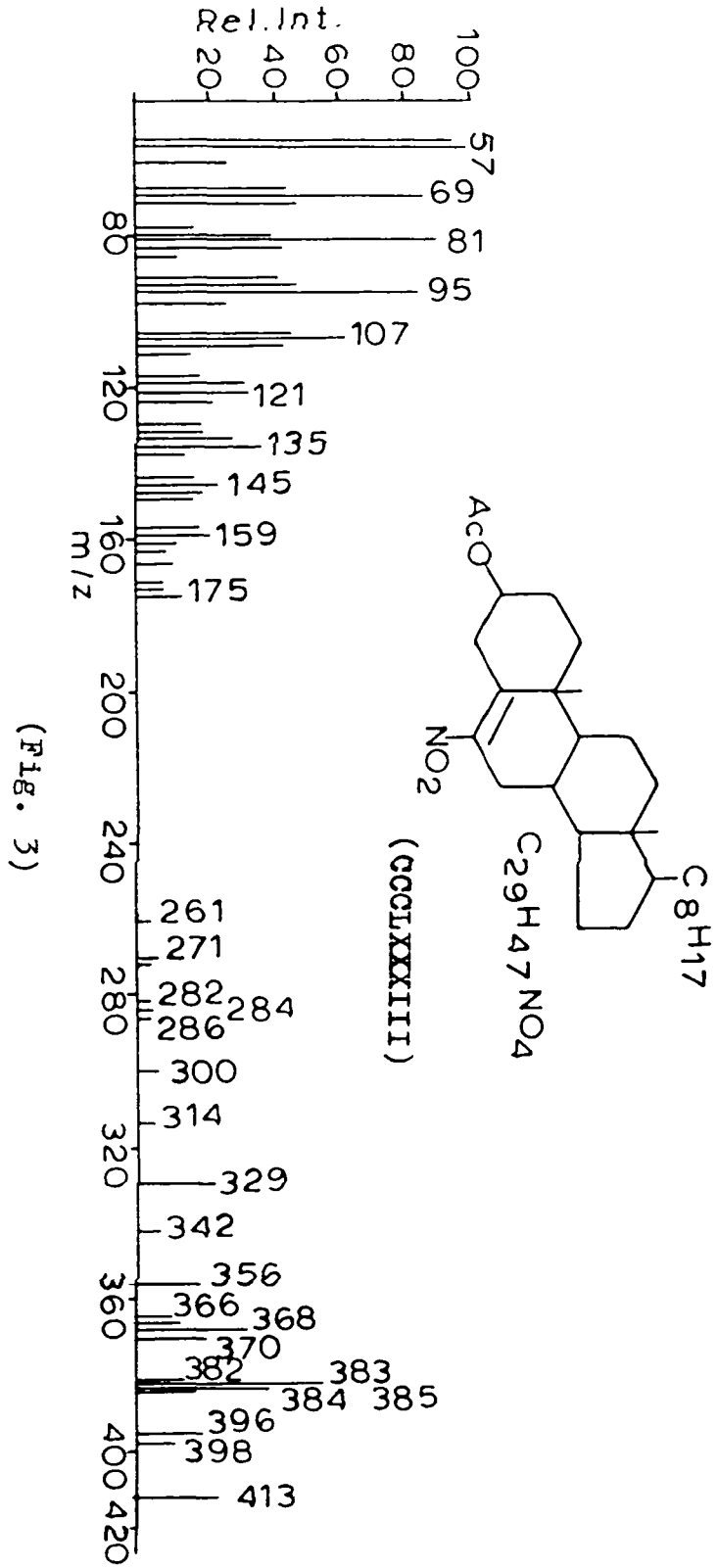

Rel.Int.
20
40
60
80
100
55
69
84
95
107
119
135
159
172
183
195
209/211
278/280
308/310
320/322
329.
336/338
356
368
370
381-383
396
398
403/405
413
416/418
419/421
432/434
434/436
449/451
80
120
160
200
240
280
320
360
400
440
460
m/z
Cl
NO2
C8H17
C27H44NO2Cl
(CCCLXXXII)

(Fig. 2)

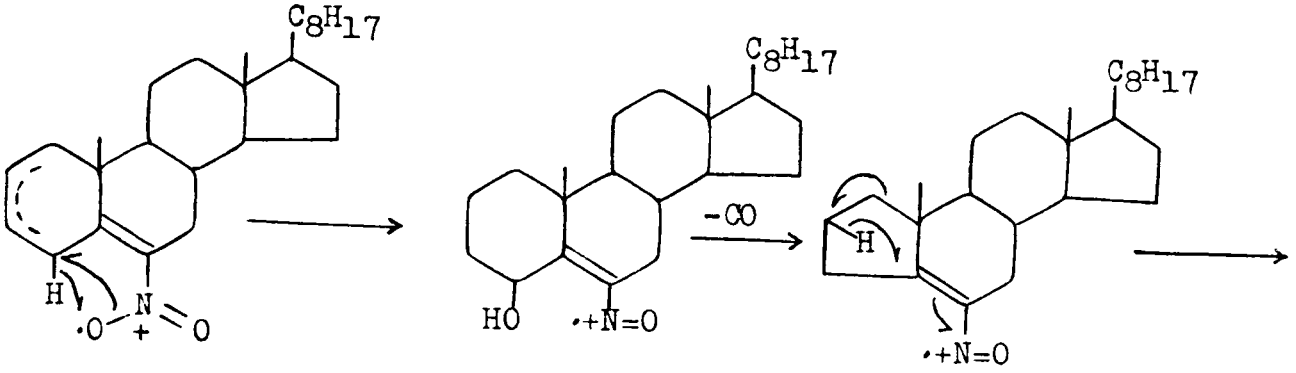

C8H17
+N = O
m/z 382
C8H17
Cl
NO2
(CCCLXXXII)
-O
-HCl
C8H17
-·CH3
NO2
m/z 398
C8H17
NO2
m/z 413
C8H17
+N——O
m/z 396
-HO·
-·NO
C8H17
·+N=O
m/z 381
C8H17
O
m/z 383
-·CH3
C8H17
O +
m/z 368

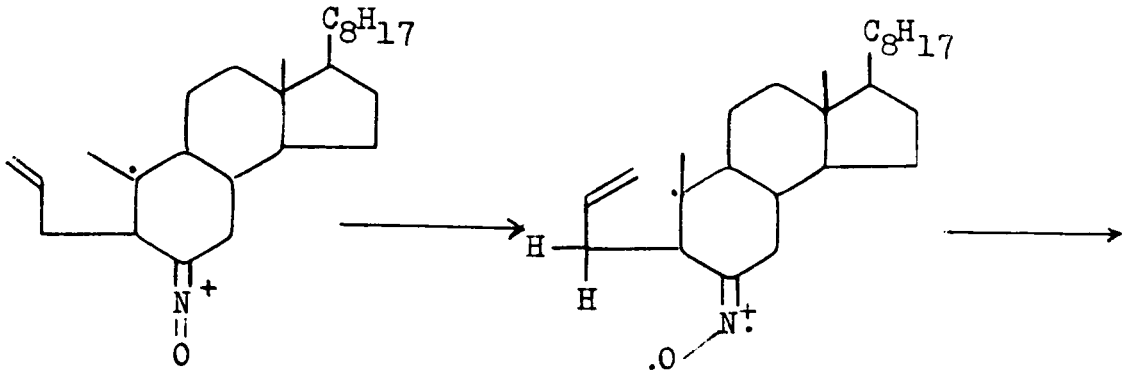
The mass spectrum of 3β-acetoxy-6-nitrocholest-5-ene (CCCLXXXIII)[135] (Fig. 3) was quite similar to that of (CCCLXXXI). The highest mass peak in this spectrum was observed at m/z 413 which was most probably due to the initial loss of a molecule of acetic acid from the molecular ion (m/z 473) by a 1,2-elimination[136]. The genesis of some of the salient fragment ions are shown in scheme.

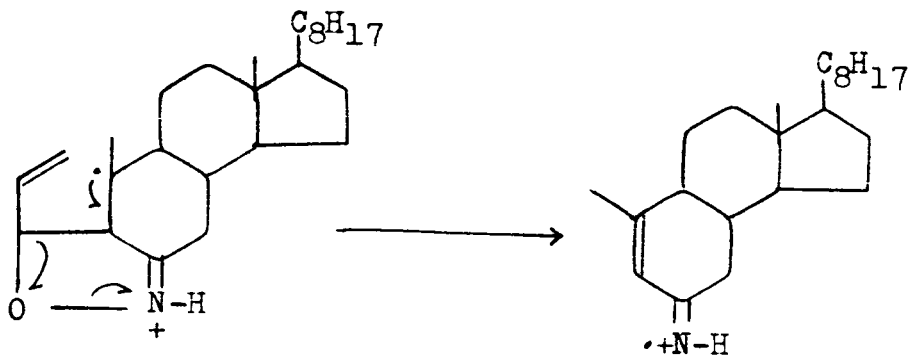



Rel.Int.
20
40
60
80
100
57
69
81
95
107
121
135
145
159
175
261
271
282
284
286
300
314
329
342
356
366
368
370
382
383
384
385
396
398
413
80
120
160
200
240
280
320
360
400
420
m/z
AcO
NO2
C29H47NO4
(CCCLXXXIII)
C8H17

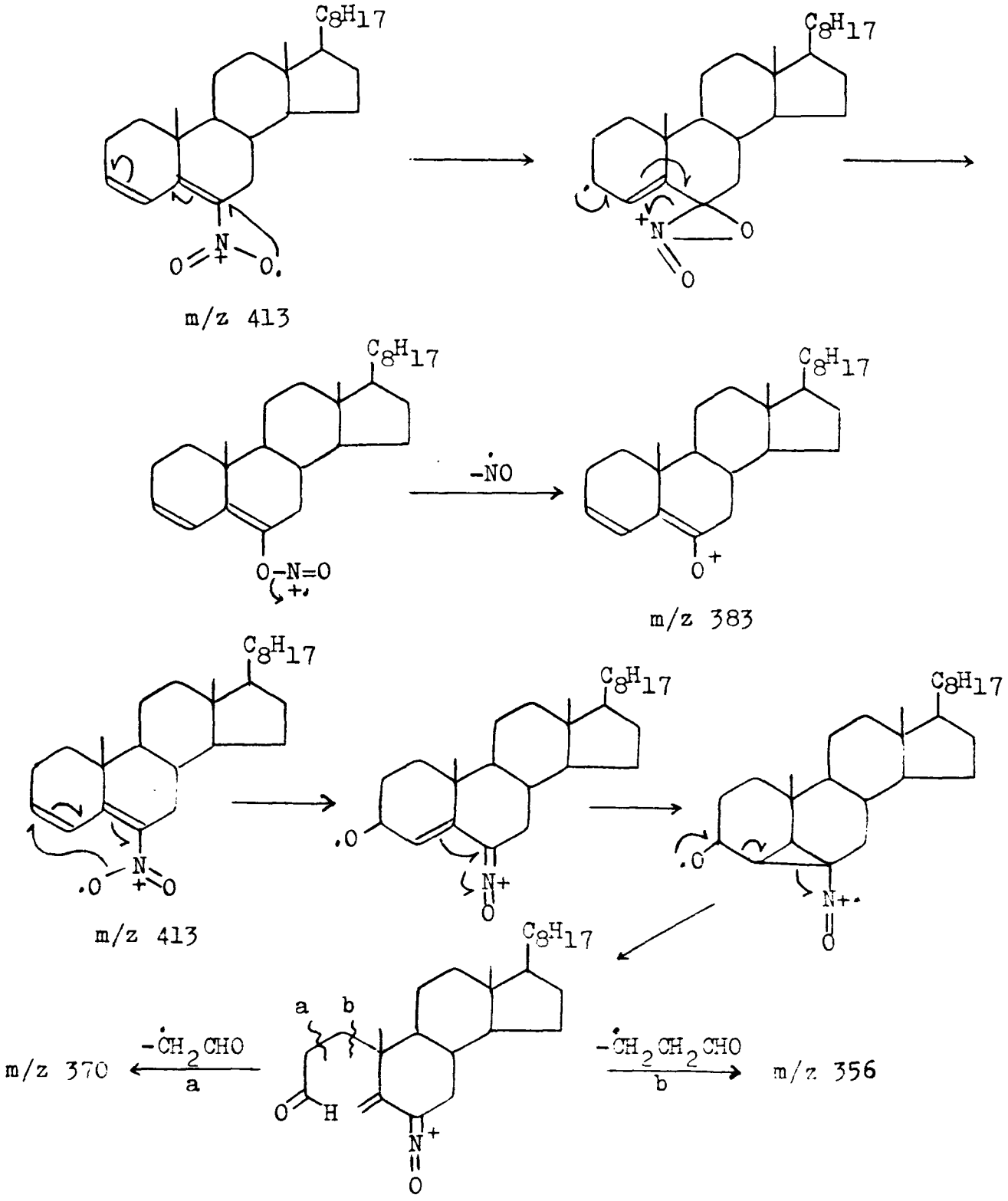
(Fig. 3)







m/z 329


C8H17
m/z 413
-ṄO
m/z 383
m/z 413
a
b
m/z 370
-ĊH2CHO
a
-ĊH2CH2CHO
b
m/z 356

EXPERIMENTAL

All melting points are uncorrected. IR spectra were determined in nujol with a Perkin-Elmer 621 and Pye Unicam SP3 100 spectrophotometers. NMR spectra were run in $CDCl_3$ on a Varian A-60D instrument with TMS as internal standard. Thin layer chromatographic plates were coated with silica gel G and sprayed with 20% aqueous perchloric acid. Light petroleum refers to a fraction of b.p. 60-80°. NMR values are given in ppm (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, umc = unresolved multiplet centred at; mc = multiplet centred at). IR values are given in cm^{-1} (s = strong, m = medium, w = weak, br = broad).

3β-Chlorocholest-5-ene (CCCIX)

Freshly purified thionylchloride (40 ml) was added gradually to cholesterol (50 g) at room temperature. A vigorous reaction ensued with the evolution of gaseous products. When the reaction slackened, the mixture was gently heated at a temperature 50-60° on a water bath for 1 hour and then poured onto crushed ice with stirring. The yellow solid thus obtained was filtered under suction and washed several times with ice-cooled water and air

dried. Recrystallization from acetone gave 3β-chlorocholest-5-ene (CCCIX) (48 g), m.p. 95-96° (lit.[137] m.p. 96-97°).

Cholest-5-ene (CCCVIII)

3β-Chlorocholest-5-ene (CCCIX) (20 g) was dissolved in warm amyl alcohol (460 ml) and sodium metal (40 g) was added to the solution with continuous stirring over a period of 8 hours. The reaction mixture was warmed occasionally. When all the sodium metal was dissolved, the reaction mixture was poured into water acidified with hydrochloric acid and then allowed to stand over night. A white crystalline solid thus obtained was filtered under suction and washed thoroughly with water and air dried. The crude material was recrystallized from acetone to provide cholest-5-ene (CCCVIII) (12 g), m.p. 94° (lit.[138], m.p. 95°).

Reaction of cholest-5-ene (CCCVIII) with acetic anhydride and zinc chloride : 6α-Acetylcholest-4-ene (CCCXIII)

A solution of cholest-5-ene (CCCVIII) (2 g) in carbon tetrachloride (40 ml) was added, in small portions, to a well stirred homogeneous solution of acetic anhydride (20 ml) and dry zinc chloride (1 g) over a period of 40 minutes. The temperature of the reaction mixture during addition was maintained between 0-5° by external cooling. After the addition was complete, stirring was continued for a period of 8 hours

under anhydrous conditions at the same temperature (0-5°). The reaction mixture was poured into ice-cooled water and extracted with carbon tetrachloride. The organic layer was washed with water, $NaHCO_3$ (5%) and water, and dried over anhydrous sodium sulphate. Evaporation of the solvent gave an oil which was purified by column chromatography. Elution with light petroleum-ether (80:1) gave the compound (CCCXIII) as an oil which was crystallized from methanol-ether mixture (700 mg) m.p. 126°; $\nu_{max.}$ 1705 (C=O), 1650 cm^{-1} (C=C); δ 4.95 m(1H, C_4-H), 3.1 br,m(1H, $C_6\beta$-H; $W_{\frac{1}{2}}$ 9 Hz), 2.0 (3H, CH_3CO), 1.03 (C_{10}-CH_3), 0.9, 0.8 and 0.65 (other methyl groups).

Analysis Found : C, 84.29; H, 11.68

$C_{29}H_{48}O$ requires : C, 84.39; H, 11.72%.

Reaction of 6α-acetylcholest-4-ene (CCCXIII) with sodium methoxide Inseparable oily mixture of 6-acetylcholest-5-ene (CCCXIV) and cholest-5-ene 5,6-ketene adduct (CCCXV)

Sodium metal (1.5 g) was dissolved in cold absolute methanol (30 ml) and to this solution 6α-acetylcholest-4-ene (CCCXIII) (1 g) was added in portions. The reaction mixture was refluxed under anhydrous conditions for 1 hour. The reaction mixture was then poured into water and extracted with ether. The ethereal layer was washed successively with water, $NaHCO_3$ (5%), water and dried over anhydrous sodium sulphate. Removal of the

solvent furnished an oily mixture of (CCCXIV) and (CCCXV) [could not be separated by chromatography over silica gel];(650 mg): $\nu_{max.}$ 1770 (four membered ring ketone), 1685 (C=O-C=O), 1650 cm^{-1} (C=C); δ 3.1 m(1H, $C_6\beta$-H; $W_{\frac{1}{2}}$ 8 Hz), 2.05 s(3H, -COCH$_3$), 1.1, 0.9, 0.8 and 0.7 (other methyl groups).

Analysis Found : C, 84.39; H, 11.71

$C_{29}H_{48}O$ requires : C, 84.39; H, 11.72%.

Reaction of 6α-acetylcholest-4-ene (CCCXIII) with hydroxyl amine hydrochloride and sodium acetate trihydrate : 6α-Acetyl-cholest-4-en-1'-oxime (CCCXVI)

A mixture of 6α-acetylcholest-4-ene (CCCXIII) (2 g), ethanol (120 ml) hydroxylamine hydrochloride (2 g) and sodium acetate trihydrate (3.5 g) was heated under reflux for 2 hours. Excess of the solvent was removed by distillation under reduced pressure and the residue was poured into cold water. The organic matter was extracted with ether. The ethereal layer was washed with water and dried over anhydrous sodium sulphate. Evaporation of the solvent gave the oxime (CCCXVI) as an oil;(700mg $\nu_{max.}$ 3280 (-OH), 1640 (C=N), 1620 cm^{-1} (C=C); δ 5.0 m(1H, C_4-H), 3.0 m(1H, $C_6\beta$-H; $W_{\frac{1}{2}}$ 8 Hz), 1.8 s(3H, CH$_3$-C=NOH), 1.43, 1.33, 1.26, 0.95 and 0.83 (other methyl groups).

Analysis Found : C, 81.38; H, 11.41; N, 3.18

$C_{29}H_{49}NO$ requires : C, 81.43; H, 11.54; N, 3.27%.

Reaction of cholest-5-ene (CCCVIII) with propionic anhydride and zinc chloride : 6β-Propanylcholest-4-ene (CCCXVIII)

A solution of cholest-5-ene (CCCVIII) (2 g) in carbon tetrachloride (40 ml) was added in small portions to a well stirred homogeneous solution of propionic anhydride (20 ml) and dry zinc chloride (1 g), over a period of 40 minutes. The temperature of the reaction mixture during addition was maintained between 0-5° by external cooling. After the addition was complete, stirring was continued for a period of 6 hours under anhydrous conditions at the same temperature (0-5°). The reaction mixture was poured into ice-cooled water and extracted with carbon tetrachloride. The organic layer was washed with water, $NaHCO_3$ (5%) and water and dried over anhydrous sodium sulphate. Evaporation of the solvent gave an oil which was crystallized from methanol-ether mixture (750 mg), m.p. 99°; $\nu_{max.}$ 1710 (C=O), 1650 cm^{-1} (C=C); δ 5.65 m(1H, C_4-H), 2.8 m (1H, $C_6\alpha$-H, $W_{\frac{1}{2}}$ 3 Hz), 2.4 q(2H, $-CO-CH_2-CH_3$, J 7.5 Hz), 1.8, 1.63, 1.2, 1.08, 0.85 and 0.7 (methyl groups).

Analysis Found : C, 84.41; H, 11.79

$C_{30}H_{50}O$ requires : C, 84.43: H, 11.81%.

Reaction of 6β-propanylcholest-4-ene (CCCXVIII) with sodium methoxide : 6α-Propanylcholest-4-ene (CCCXIX)

Sodium metal (1.5 g) was dissolved in cold absolute methanol (30 ml) and to this solution 6β-propanylcholest-4-ene (CCCXVIII) (1 g) was added in small portions. The reaction mixture was refluxed on a water bath under anhydrous conditions for 1 hour. The reaction mixture was poured into water and extracted with ether. The ethereal layer was washed successively with water, $NaHCO_3$ (5%), water and dried over anhydrous sodium sulphate. Removal of the solvent furnished (CCCXIX) as an oil which was crystallized from methanol-ether mixture (400 mg), m.p. 112°; $\nu_{max.}$ 1710 (C=O), 1650 cm^{-1} (C=C); δ 4.88 m(1H, C_4-H), 3.13 m (1H, $C_6\beta$-H, $W_{\frac{1}{2}}$ 9 Hz), 2.4 q(2H, $-COCH_2-CH_3$, J=7 Hz), 1.8, 1.63, 1.2, 1.08, 0.85 and 0.7 (methyl groups).

Analysis Found : C, 84.39; H, 11.82

$C_{30}H_{50}O$ requires : C, 84.43; H, 11.81%.

Reaction of 6β-propanylcholest-4-ene (CCCXVIII) with hydroxylamine hydrochloride and sodium acetate trihydrate : 6-Propanylcholest-5-en-1'-oxime (CCCXXII)

A mixture of the β,γ-unsaturated ketone (CCCXVIII) (1 g), hydroxylamine hydrochloride (1 g), sodium acetate trihydrate (1.5 g) and ethanol (40 ml) was heated under reflux for 2 hours.

Excess of the solvent was removed by distillation under reduced pressure and the residue was diluted with ice-cooled water. The crude oxime (CCCXXII) thus obtained as solid was filtered, washed with water, air dried and crystallized from methanol (750 mg), m.p. 187°; $\nu_{max.}$ 3280 (-OH), 1660 cm^{-1} (C=N and C=C), δ 3.25 m(1H, HON=C(H)-CH-CH_3), 1.23, 1.2, 0.93, 0.85 and 0.77 (methyl groups).

Analysis Found : C, 81.59; H, 11.59; N, 3.11

$C_{30}H_{51}NO$ requires : C, 81.56; H, 11.63; N, 3.17%.

Reaction of 3β-chlorocholest-5-ene (CCCIX) with acetic anhydride and zinc chloride : 3β-Acetoxycholest-5-ene (CCCX)

A solution of 3β-chlorocholest-5-ene (CCCIX) (1 g) in carbon tetra chloride (30 ml) was added in small portions to a well stirred homogeneous solution of acetic anhydride (10 ml) and dry zinc chloride over a period of 40 minutes. The temperature of the reaction mixture during addition was maintained between 0-5° by external cooling. After the addition was complete, stirring was continued for a period of 9 hours under anhydrous conditions at the same temperature (0-5°). The reaction mixture was poured into ice-cooled water and extracted with carbon tetra chloride. The organic layer was washed with water, $NaHCO_3$ (5%) and water and dried over anhydrous sodium sulphate. Evaporation of the solvent furnished 3β-acetoxycholest-5-ene (CCCX) as an

oil, which was crystallized from acetone (550 mg), m.p. and m.m.p. 115° (lit.[111] m.p. 116°).

Reaction of 3β-chlorocholest-5-ene (CCCIX) with propionic anhydride and zinc chloride : 3β-Propionoxycholest-5-ene (CCCXXIII)

A solution of 3β-chlorocholest-5-ene (CCCIX) (2 g) in carbon tetra chloride (40 ml) was added in small portions to a well stirred homogeneous solution of propionic anhydride (20 ml) and dry zinc chloride (1 g) over a period of 40 minutes. The temperature of the reaction mixture during addition was maintained between 0-5° by external cooling. After the addition was complete, the stirring was continued for a period of 9 hours under anhydrous conditions at the same temperature (0-5°). The reaction mixture was diluted with ice-cooled water and then extracted with carbon tetrachloride in usual way. Washing of organic layer during work up was done with water, $NaHCO_3$ (5%) and water and dried over anhydrous sodium sulphate. Removal of the solvent afforded (CCCXXIII) as an oil which was crystallized from acetone (600 mg), m.p. 100° (lit.[112] m.p. 100°); $\nu_{max.}$ 1730 (CH_3-CH_2-O-), 1200 cm^{-1} (C-O); δ 5.3 br(1H, C_6-H), 4.53 br(1H, $C_3\alpha$-H), 2.2 q(2H, CH_3-CH_2-COO-), 1.2, 1.08, 1.01, 0.91, 0.83 and 0.68 (methyl groups).

3β-Acetoxycholest-5-ene (CCCX)

A mixture of cholesterol (50 g), pyridine (75 ml) and acetic anhydride (50 ml) was heated on a water bath for 2 hours. The resulting brown solution was poured onto crushed ice water mixture with stirring. A light brown solid thus obtained was filtered under suction, washed with water and air dried. The crude product on recrystallization from acetone gave pure 3β-acetoxycholest-5-ene (CCCX) (45 g), m.p. 114-115° (lit.[111] m.p. 116°).

Reaction of 3β-acetoxycholest-5-ene (CCCX) with acetic anhydride and zinc chloride

A solution of 3β-acetoxycholest-5-ene (CCCX) (1 g) in carbon tetrachloride (30 ml) was added in small portions to a well stirred homogeneous solution of acetic anhydride (10 ml) and dry zinc chloride (0.5 g) over a period of 40 minutes. The temperature of the reaction mixture during addition was maintained between 0-5° by external cooling. After the addition was complete stirring was continued for a period of 9 hours under anhydrous conditions at the same temperature (0.5°). The reaction mixture was worked up with carbon tetrachloride, washed with water, $NaHCO_3$ (5%) and water and dried over anhydrous sodium sulphate. Evaporation of the solvent gave 3β-acetoxycholest-5-ene (CCCX), the starting olefin as an oil which was crystallized from acetone

(900 mg), m.p. and m.m.p. 115° (lit.[111] m.p. 116°).

Reaction of 3β-acetoxycholest-5-ene (CCCX) with propionic anhydride and zinc chloride

A solution of 3β-acetoxycholest-5-ene (CCCX) (1 g) in carbon tetrachloride (30 ml) was added in small portions to a well stirred homogeneous solution of propionic anhydride (10 ml) and dry zinc chloride (0.5 g) over a period of 40 minutes. The temperature of the reaction mixture during addition was maintained 0-5° by external cooling. After the addition was complete, stirring was continued for a period of 9 hours under anhydrous conditions at the same temperature (0-5°). The reaction mixture was worked up in usual manner with carbon tetrachloride, washed with water, $NaHCO_3$ (5%) and water and dried over anhydrous sodium sulphate. Evaporation of the solvent afforded 3β-acetoxy-cholest-5-ene (CCCX), the starting olefin as an oil which was crystallized from acetone (850 mg), m.p. and m.m.p. 115°(lit.[111] m.p. 116°).

3β-Hydroxy-5,6β-dibromo-5α-cholestane

To a solution of cholesterol (14 g) in ether (100 ml) was added gradually bromine solution (5 ml bromine dissolved in 100 ml glacial acetic acid containing 2 g of anhydrous sodium acetate) with stirring. The solution turned yellow and promptly

set to a stiff paste of dibromide. The mixture was cooled and stirred with a glass rod for five minutes to ensure complete crystallization. The product was then filtered under suction and washed with cold ether-acetic acid (3:7) mixture until the filtrate was competely colourless. The white dibromide was air dried (15 g), m.p. 112-113° (lit.[113] m.p. 113°).

5,6β-Dibromo-5α-cholestan-3-one

3β-Hydroxy-5,6β-dibromo-5α-cholestane (10 g) was suspended in acetone (300 ml) in a three necked flask fitted with a stirrer and a dropping funnel. The suspension was stirred for five minutes and Jones' reagent (15 ml) was then added dropwise from a dropping funnel in the course of 15 minutes. The temperature of the reaction mixture was maintained between 0-5° by external cooling during oxidation. After the addition was complete, stirring was continued for additional 15 minutes and cold water (200 ml) was then added. The product thus obtained was filtered under suction, washed thoroughly with water and air dried to give the dibromo ketone (8.5 g), m.p. 73-75° (lit.[113] m.p. 75°).

Cholest-5-en-3-one (CCCXI)

5,6β-Dibromo-5α-cholestan-3-one (5 g) was dissolved in ether (100 ml) and glacial acetic acid (2.5 ml). Zinc dust (7.5 g) was then added in small portions during 30 minutes with

continuous shaking. After the complete addition, the ethereal layer containing suspended zinc dust was filtered, washed successively with water, $NaHCO_3$ (5%) and again with water and dried over anhydrous sodium sulphate. Removal of the solvent provided an oil which was crystallized from methanol to give cholest-5-en-3-one (CCCXI) (3 g), m.p. 126° (lit.[113] m.p. 129°); $\gamma_{max.}$ 1705 (C=O), 1620 cm^{-1} (C=C).

Reaction of cholest-5-en-3-one (CCCXI) with acetic anhydride and zinc chloride : Cholest-4-en-3-one (LXXVIII), cholest-4-ene-3,6-dione (CXII) and 6ε-acetylcholest-4-en-3-one (CCCXXIV)

A solution of cholest-5-en-3-one (CCCXI) (3 g) in carbon tetrachloride (60 ml) was added in small portions to a well stirred homogeneous solution of acetic anhydride (30 ml) and dry zinc chloride (1.5 g) over a period of 40 minutes. The temperature of the reaction mixture during addition was maintained between 0-5° by external cooling. After the addition was complete, stirring was continued for a period of 6 hours under anhydrous conditions at the same temperature (0-5°). The reaction mixture was poured into ice-cooled water and extracted with carbon tetrachloride. The organic layer was washed with water, $NaHCO_3$ (5%) and water, and dried over anhydrous sodium sulphate. Evaporation of the solvent gave an oil which was chromatographed over silica gel (60 g), each fraction of 25 ml was coolected. Elution with light petroleum-ether (25:1)

furnished a solid compound which was crystallized from ethanol to give cholest-4-en-3-one (LXXVIII) (300 mg), m.p. 80° (lit.[113] m.p. 81-82°); $\nu_{max.}$ 1680 (C=C-C=O), 1620 cm^{-1} (C=C); δ 5.66 s (1H, C_4-H), 2.3 m(2H, C_2-H_2), 1.6, 0.9, 0.8 and 0.77 (methyl groups).

Further elution with light petroleum-ether (20:1) gave cholest-4-ene-3,6-dione (CXII), crystallized from methanol (250 mg), m.p. 123° (lit.[114] m.p. 123°); $\nu_{max.}$ 1680 (C=C-C=O), 1615 cm^{-1} (C=C); δ 6.16 s(1H, C_4-H), 2.6 m(4H, C_2-H_2 C_7-H_2), 1.16, 0.96, 0.90, 0.84 and 0.72 (methyl groups).

Elution with light petroleum-ether (16:1) afforded 6ξ-acetylcholest-4-en-3-one (CCCXXIV), crystallized from methanol (600 mg), m.p. 100°; $\nu_{max.}$ 1710 (C=O), 1680 (C=C-C=O), 1615 cm^{-1} (C=C); δ 5.96 s(1H, C_4-H), 3.2 m(1H. $C_6\xi$-H, $W_{\frac{1}{2}}$ 9 Hz), 2.13 s (3H, CH_3-CO-), 1.25 s(C_{10}-CH_3), 1.0, 0.9, 0.8 and 0.7 (other methyl groups).

Analysis Found : C, 81.61; H, 10.78

$C_{29}H_{46}O_2$ requires : C, 81.63; H, 10.86%.

Reaction of 6ξ-acetylcholest-4-en-3-one (CCCXXIV) with hydroxylamine hydrochloride and sodium acetate trihydrate : 6-Acetylcholest-5-en-3-one-1',3-dioxime (CCCXXVII)

A mixture of 6ξ-acetylcholest-4-en-3-one (CCCXXIV) (2 g),

hydroxylamine hydrochloride (3.5 g), sodium acetate trihydrate (4 g) and ethanol (120 ml) was heated under reflux on a water bath for 2 hours. Excess of the solvent was removed by distillation under reduced pressure and the residue was diluted with ice-cooled water. The crude oxime (CCCXXVII) thus obtained as solid was filtered, washed with water and air dried. It was purified by column chromatography over silica gel (40 g). Elution with light petroleum-ether (10:1) provided (CCCXXVII) which was crystallized from methanol (500 mg), m.p. 145°; $\nu_{max.}$ 3240 (-OH), 1650 (C=N), 1630 cm^{-1} (C=C); δ 7.0 br(2H, -N-O-H), 2.1 br,s(3H, CH_3-C=NOH), 1.2, 0.91, 0.8 and 0.6 (other methyl groups).

Analysis Found : C, 76.22; H, 10.51; N, 6.08

$C_{29}H_{48}N_2O_2$ requires : C, 76.26; H, 10.59; N, 6.13%.

Reaction of cholest-5-en-3-one (CCCXI) with propionic anhydride and zinc chloride : Cholest-4-en-3-one (LXXVIII) and 6β-propionoxy-cholest-4-en-3-one (CCCXXX)

A solution of cholest-5-en-3-one (CCCXI) (3 g) in carbon tetrachloride (60 ml) was added in small portions to a well stirred homogeneous solution of propionic anhydride (30 ml) and dry zinc chloride (1.5 g) over a period of 40 minutes. The temperature of the reaction mixture during addition was maintained between 0-5° by external cooling. After the addition was complete, stirring was continued at 0-5° for a period of 5 hours

under complete anhydrous conditions. The reaction mixture was poured into ice-cooled water and extracted with carbon tetrachloride. The organic layer was washed with water, $NaHCO_3$ (5%) and water, and dried over anhydrous sodium sulphate. Evaporation of the solvent provided an oil which was chromatographed over silica gel (60 g), each fraction of 25 ml collected. Elution with light petroleum-ether (20:1) gave a solid compound which was crystallized from ethanol to give cholest-4-en-3-one (LXXVIII) (300 mg), m.p. 80° (lit.[113] m.p. 81-82°).

Further elution with light petroleum-ether (18:1) afforded 6ξ-propionoxycholest-4-en-3-one (CCCXXX), crystallized from methanol (700 mg), m.p. 119°; $\nu_{max.}$ 1740 (O-COC_2H_5), 1680 (C=C-C=O); δ 5.7 s(1H, C_4-H), 5.45m(1H, C_6ξ-H, $W_{\frac{1}{2}}$ 9 Hz), 2.36 br,m(4H, C_2-H_2 and CH_3-CH_2-CO-O-), 1.18, 1.1, 0.9, 0.8 and 0.7 (methyl groups).

Analysis Found : C, 78.81; H, 10.49

$C_{30}H_{48}O_3$ requires : C, 78.89; H, 10.59%.

<u>Beckman rearrangement of 6-acetylcholest-5-en-3-one-1',3-dioxime (CCCXXVII) ; 6ξ-N-acetamido-4-aza-A-homocholest-4a-en-3-one (CCCXXXI) and 4-aza-A-homocholest-5-en-3-one 5,6-ketene adduct (CCCXXXV)</u>

The dioxime (CCCXXVII) (2 g) was added as quickly as possible, with stirring, to thionylchloride (20 ml) at 0° and

the solution was immediately poured into 4N potassium hydroxide solution (190 ml) kept at 80°. A solid thus obtained was filtered under suction, washed with water and air dried. The crude product thus obtained was subjected to column chromatography over silica gel (40 g). Each fraction of 20 ml was collected. Elution with light petroleum-ether (8:1) gave (CCCXXXI), crystallized from methanol (700 mg), m.p. 240°; $\nu_{max.}$ 3360 (NH), 1660 (CONH), 1610 cm^{-1} (C=C); δ 6.4 br(2H, two CONH; exchangeable with deuterium), 5.83 br, s(1H, C_{4a}-vinylic proton), 3.2 m(1H, $C_6\beta$-H, $W_{\frac{1}{2}}$ 9 Hz), 2.4 m(2H, C_2-H_2), 2.0 s(3H, CH_3-CONH), 1.05, 0.85, 0.78 and 0.6 (other methyl groups).

Analysis Found : C, 76.2°; H, 10.55; N, 6.13

$C_{29}H_{48}N_2O_2$ requires : C, 76.26; H, 10.59; N, 6.13%.

Further elution with light petroleum-ether (6:1) provided (CCCXXXV) as homogeneous oil 'A' (300 mg); $\nu_{max.}$ 3200 (NH), 1770 (four membered ring ketone), 1660 cm^{-1} (CONH); δ 6.5 s(1H, CONHβ exchangeable with deuterium), 4.2 m(2H, C_{4a}-H_2), 3.13 m (1H, $C_6\beta$-H, $W_{\frac{1}{2}}$ 8Hz), 2.4 m(2H, C_2-H_2), 1.26, 0.86, 0.8 and 0.56 (methyl groups).

Analysis Found : C, 78.8°; H, 10.61; N, 3.12

$C_{29}H_{47}NO_2$ requires : C, 78.85; H, 10.72. N, 3.17%.

Schmidt reaction of 6ξ-acetylcholest-4-en-3-one (CCCXXIV) : 6ξ-N-acetamido-3-aza-A-homocholest-4a-en-4-one (CCCXXXII)

A mixture of 6ξ-acetylcholest-4-en-3-one (CCCXXIV) (2 g) and polyphosphoric acid [from P_2O_5 (30 g) and H_3PO_4 (20 ml)] was heated on a water bath, sodium azide (500 mg) was added in small portions and heated further for 8 hours. Then the reaction mixture was poured into ice-cooled water and extracted with chloroform (3x100 ml) and washed successively with water, $NaHCO_3$ (5%) and again with water, dried over anhydrous sodium sulphate. Excess of the solvent was removed under reduced pressure to give an oil (CCCXXXII) which was crystallized from methanol (650 mg), m.p. 172°; $\nu_{max.}$ 3300 (NH), 1670, 1640 (CONH), 1610 cm^{-1} (C=C); δ 7.0 br(2H, two CONH; exchangeable with deuterium), 5.8 s(1H, C_{4a}-vinylic proton), 4.5 m(2H, C_2-H_2), 3.2 m(1H, $C_{6\xi}$-H, $W_{\frac{1}{2}}$ 9 Hz), 2.0 s(3H, CH_3-CONH), 1.08, 0.9, 0.8 and 0.7 (other methyl groups).

Analysis Found : C, 76.23; H, 10.50; N, 6.11

$C_{29}H_{48}N_2O_2$ requires : C, 76.26; H, 10.59; N, 6.13%.

Cholest-4-en-3-one (LXXVIII)

A solution of cholest-5-en-3-one (CCCXI) (3 g) in ethanol (30 ml) containing oxalic acid (0.4 g) was heated under reflux for 15 minutes. The reaction mixture was poured into cold water and extracted with ether. The ethereal solution was

washed successively with water, $NaHCO_3$ (5%) and again with water and dried over anhydrous sodium sulphate. The oily residue obtained after evaporation of the solvent, was crystallized from methanol to give the ketone (LXXVIII) (1.2 g) m.p. 80° (lit.[113] m.p. 81-82°); $\nu_{max.}$ 1680 (C=C-C=O), 1620 cm^{-1} (C=C); δ 5.66 s(1H, C_4-H), 2.3 m(2H, C_2-H_2), 1.6, 0.9, 0.8 and 0.77 (methyl groups).

Bromination of cholest-4-en-3-one (LXXVIII) : 2,6-Dibromocholesta-1,4,6-trien-3-one (CCCXXXVI)

A solution of the ketone (LXXVIII) (6 g) in acetic acid (18 ml) and ether (90 ml) was cooled in an ice bath. Bromine solution (4.1 g of bromine in 58 ml of acetic acid) was added dropwise to the cooled solution of the ketone (LXXVIII). Few drops of HBr (48%) was added to catalyse the reaction. After the complete addition of the bromine solution the reaction mixture was kept for 2 hours in cold than the precipitated 2,6-dibromocholesta-1,4,6-trien-3-one (CCCXXXVI) was filtered under suction and recrystallized from light petroleum-ether (3.6 g), m.p. 203° (lit.[115] m.p. 203°); $\nu_{max.}$ 1660 s(C=C-C(=O)-C=C), 1610 m(C=C), 760 cm^{-1} (C-Br); δ 7.23 s(1H, C_1-H), 6.46 s(1H, C_4-H), 6.3 d(1H, C_7-H), 1.28 s(3H, C_{10}-CH_3), 0.9, 0.8 and 0.73 (other methyl groups).

Analysis Found : C, 60.19; H, 6.99

$C_{27}H_{38}OBr_2$ requires : C, 60.22; H, 7.11%.

Schmidt reaction of 2,6-dibromocholesta-1,4,6-trien-3-one (CCCXXXVI) : 4-Aza-A-homo-19-nor-1-methyl-2,6-dibromocholesta-1(10),4a,6-trien-3-one (CCCXXXIX) and 4-aza-A-homo-19-nor-1-methyl-2,6-dibromocholesta-1,4a,6-trien-3-one (CCCXL)

A mixture of 2,6-dibromocholesta-1,4,6-trien-3-one (CCCXXXVI) (3 g) and polyphosphoric acid [from P_2O_5 (45 g) and H_3PO_4 (30 ml)] was heated on a water bath, sodium azide (750 mg) was added in small portions and heated further for 8 hours. Then the reaction mixture was poured into ice-cooled water and extracted with chloroform (3x100 ml) and washed successively with water, $NaHCO_3$ (5%) and again with water, dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to give an oil (2.8 g) which was chromatographed over silica gel (60 g). Elution with light petroleum-ether (10:1) furnished (CCCXXXIX) as homogeneous oil (600 mg); $\nu_{max.}$ 3500, 3200 (NH), 1670 (CONH), 1610 (C=C), 760 cm^{-1} (C-Br); δ 6.5 br,m(2H, C_{4a}-H and C_7-H), 4.3 s(1H, C_2-H), 2.4 s(3H, C_1-CH_3), 1.26, 0.96 and 0.83 (other methyl groups).

Analysis Found : C, 58.55; H, 7.08; N, 2.49

$C_{27}H_{39}NOBr_2$ requires : C, 58.59; H, 7.10; N, 2.55%.

Further elution with light petroleum-ether (6:1) provided the compound (CCCXL), crystallized from methanol (800 mg), m.p. 220°; $\nu_{max.}$ 3500, 3200 (NH), 1670 (CONH), 1610 (C=C), 760 cm^{-1} (C-Br); δ 6.66 br,m(2H, C_{4a}-H and C_7-H), 2.4 s(3H, C_1-CH_3), 1.11,

0.95 and 0.8 (other methyl groups).

Analysis Found : C, 58.54; H, 7.09; N, 2.48

$C_{27}H_{39}NOBr_2$ requires : C, 58.59; H, 7.10; N, 2.53%.

Reaction of 6ξ-acetylcholest-4-en-3-one (CCCXXIV) with an excess of hydrazoic acid : 6ξ-Acetamido-3-aza-A-homocholest-4a-eno [3,4-d]tetrazole (CCCXLII) and 6ξ-acetyl-3-aza-A-homocholest-4a-eno[3,4-d]tetrazole (CCCXLIV)

Sodium azide (3 g) was dissolved in water (15 ml) and to this was added benzene (22.5 ml) at 0°. Sulphuric acid (3 ml) was then added dropwise with shaking over a period of 30 minutes at 0-5°, shaking was continued for additional 30 minutes, and the organic layer was separated, dried over anhydrous sodium sulphate and filtered. This solution of hydrazoic acid in benzene (22.5 ml) was made upto (27.5 ml) by addition of benzene and was treated with freshly distilled boron trifluoride-etherate (1.5 ml) in the cold. To this was added a solution of the ketone (CCCXXIV) (1.5 g) in benzene (30 ml) in roughly 5 hours and this reaction mixture was kept at room temperature for 3 days. Benzene was removed by distillation under reduced pressure and the residue was dissolved in ether. The ethereal solution was washed with water, $NaHCO_3$ (10%) and water, dried over anhydrous sodium sulphate. Evaporation of the solvent gave an oil which was chromatographed over silica gel (30 g). Fractions of 25 ml were collected. Elution with light petroleum-ether (12:1) gave the

tetrazole (CCCXLII), crystallized from methanol (300 mg), m.p. 289°; $\nu_{max.}$ 3280 (NH), 1650 (CONH), 1525 (C=N), 1450, 1370 cm^{-1} (N=N); δ 6.96 s(1H, C_{4a}-H), 5.15 br(1H, CONH; exchangeable with deuterium), 4.5 m(2H, C_2-H_2), 3.0 br,m(1H, $C_6\beta$-H, $W_{\frac{1}{2}}$ 9 Hz), 2.04 s(3H, CH_3-CONH), 1.86, 1.16, 0.9 and 0.8 (other methyl groups).

Analysis Found : C, 72.26; H, 9.81; N, 14.51

$C_{29}H_{47}N_5O$ requires : C, 72.30; H, 9.83; N, 14.53%

Further elution with light petroleum-ether (8:1) furnished the tetrazole (CCCXLIV), crystallized from methanol (200 mg), m.p. 278°; $\nu_{max.}$ 1705 (C=O), 1530 (C=N), 1460, 1380 cm^{-1} (N=N), δ 6.5 (1H, C_{4a}-H), 4.2 m(2H, C_2-H_2), 3.1 (1H, $C_6\beta$-H, $W_{\frac{1}{2}}$ 8 Hz), 2.01 m(3H, CH_3CO), 1.25, 0.97, 0.9, 0.76 and 0.7 (other methyl groups).

Analysis Found : C, 74.59; H, 9.92; N, 11.98

$C_{29}H_{46}N_4O$ requires : C, 74.62; H, 9.93; N, 12.00%.

Chromic acid oxidation of cholest-5-ene (CCCVIII) : 5-Keto-5,6-secocholestan-6-oic acid and cholest-5-en-7-one (CV)

Cholest-5-ene (CCCVIII) (13 g) was dissolved in warm acetic acid (700 ml) and to this a solution of chromium trioxide (16 g) in 50% acetic acid (50 ml) was added with continuous stirring over a period of 2 hours. After the complete addition of chromic

acid solution, the reaction mixture was stirred at 70-75° for additional 2 hours. The excess of chromic acid was destroyed by addition of methanol (20 ml). The bulk of the acetic acid was removed by distillation under reduced pressure when a green viscous material was obtained. It was extracted with ether (3x150 ml) and the ethereal solution was washed with water and then extracted with sodium hydroxide solution (10%, 4x50 ml). The ether solution was washed with water and dried over anhydrous sodium sulphate. Removal of the solvent provided cholest-5-en-7-one (CV), which was purified by column chromatography over silica gel (60 g) (2.5 g), m.p. 127-130° (lit.[139] m.p. 125-129°).

The combined alkaline extract was acidified with hydrochloric acid and the liberated organic acid was extracted with ether. The ethereal solution was washed with water and dried over anhydrous sodium sulphate. After usual work up of the ether solution, an oil was obtained. This was purified by column chromatography over silica gel (100 g). The purified acid was obtained as a viscous oil[117] (3.5 g) (homogeneous by t.l.c.); $\nu_{max.}$ 3400-3200 br(COO<u>H</u>), 1715, 1705 cm^{-1} (C=O, <u>C</u>OOH); δ 10.6 s(1H, disappeared on addition of D_2O, COO<u>H</u>), 2.3 umc(4H, CO-C<u>H</u>$_2$ and C<u>H</u>$_2$-COOH), 1.0 s(3H, C_{10}-C<u>H</u>$_3$), 0.9, 0.82 and 0.7 (other methyl groups).

Methyl 5-keto-5,6-secocholestan-6-oate (CCCXLV)

5-Keto-5,6-secocholestan-6-oic acid (500 mg) was dissolved in ether and the solution was cooled in an ice bath. To this, excess of an ethereal solution of diazomethane was added till a yellow colour persisted. The reaction mixture was kept in the cold for 15 minutes and the excess of diazomethane was decomposed by dilute acetic acid. The ethereal solution was washed with water, sodium bicarbonate solution (5%) and water and dried over anhydrous sodium sulphate. Removal of the solvent provided the desired methyl ester (CCCXLV), which was crystallized from methanol in the cold (400 mg), m.p. 102-103° (lit.[117] m.p. 102-103°); $\nu_{max.}$ 1735 s($\underline{C}OOCH_3$), 1708 cm^{-1} (C=O); δ (100 MHz), 3.56 s(3H, $COOC\underline{H}_3$), 2.2 umc (4H, $CO\underline{CH}_2$ and $\underline{CH}_2COOCH_3$) 1.0 s(3H, $C_{10}-C\underline{H}_3$), 0.9, 0.83 and 0.68 (other methyl groups).

Reaction of methyl 5-keto-5,6-secocholestan-6-oate (CCCXLV) with an excess of hydrazoic acid : Methyl 5,6-seco-4a-aza-A-homocholestan[5a,5-d]tetrazole-6-oate (CCCXLVII)

To a solution of hydrazoic acid (20 ml) [prepared as described earlier] was added boron trifluoride-etherate (1 ml) in the cold. To this, was added a solution of the ester (CCCXLV) (1 g) in benzene (20 ml) in about 5 hours and this reaction mixture was kept at room temperature for 3 days. Benzene was removed by distillation under reduced pressure and the residue

was dissolved in ether. The ethereal solution was washed with water, $NaHCO_3$ (10%) and water and dried over anhydrous sodium sulphate. Evaporation of the sovent gave an oil which was chromatographed over silica gel (20 g). Elution with light petroleum-ether (8:1) provided the tetrazole (CCCXLVII), crystallized from light petroleum (400 mg), m.p. 148°; ν_{max} 1730 ($-\underline{C}OOCH_3$), 1520 (C=N), 1460, 1375 cm^{-1} (N=N); δ 3.31 s(3H, $-C\underline{H}_3-O-C-$), 3.08 m(2H, $C_4-\underline{H}_2$), 2.8 m(2H, $C_7-\underline{H}_2$), 1.78 s(3H, $C_{10}-C\underline{H}_3$), 1.18, 0.91, 0.8 and 0.7 (other methyl groups).

Analysis Found : C, 71.15; H, 10.21; N, 11.83

$C_{28}H_{48}N_4O_2$ requires : C, 71.14; H, 10.23; N, 11.85%.

3β-Acetoxy-5,6-secocholestan-5-keto-6-oic acid

To a well stirred mixture of 3β-acetoxycholest-5-ene (CCCX) (54 g) and glacial acetic acid (600 ml) a solution of chromium trioxide (35 g) in 50% acetic acid (100 ml) was added over a period of 2 hours and the reaction mixture was maintained at 55-60° throughout. After complete addition, the mixture was stirred for additional 2 hours at the same temperature. The excess of chromic acid was destroyed by the addition of methanol (30 ml) and then acetic acid (400 ml) was removed by distillation under reduced pressure. The remaining liquid was diluted with water (25 ml) and allowed to stand in the cold for 12 hours. The crystalline 3β-acetoxycholest-5-en-7-one (CIV), separated as

plates, was removed by filtration under suction and washed with acetic acid (80%, 50 ml) (16 g), m.p. 152-155°. Several recrystallizations from methanol raised the m.p. to 161-163° (lit.[140] m.p. 164°); $\nu_{max.}$ 1734 s($CH_3\underline{COO}$), 1608 s(C=C-C=O), 1630 m(C=C-C=O), 1235 cm^{-1} (acetate); δ (100 MHz), 5.65 s(1H, C_6-$\underline{H}$), 4.7 br(1H, $C_3\alpha$-$\underline{H}$), 2.0 s(3H, $C\underline{H}_3COO$), 1.08 s(3H, C_{10}-$C\underline{H}_3$), 0.68 s(3H, C_{13}-$C\underline{H}_3$), 0.89, 0.82, 0.78 (other methyl groups).

The filtrate was diluted with 50% methanol water (70 ml), seeded with a sample of 3β-acetoxy-5,6-secocholestan-5-keto-6-oic acid and placed in refrigerator for a period of 10-12 days. The seco acid crystallized out as a thick green coloured mass was filtered under suction and washed with 75% acetic acid (100 ml). The crude material (13 g) melted at 116-119°. Several recrystallizations from methanol raised the m.p. to 127-129° (lit.[111,141] 127-129°); (Found: C, 73.32; H, 10.42. Cacld. for $C_{29}H_{48}O_5$; C, 73.07; H, 10.15%); $\nu_{max.}$ 3350-3200 br(COO$\underline{H}$), 1738 s($CH_3\underline{CO}O$), 1712 ($\underline{CO}OH$), 1240 cm^{-1} (acetate); δ (100 MHz), 9.8 s(1H, exchangeable with deuterium, COO$\underline{H}$), 5.3 br(1H, $C_3\alpha$-$\underline{H}$), 2.0 s(3H, $C\underline{H}_3COO$), 1.01 s(3H, C_{10}-$C\underline{H}_3$), 0.7 s(3H, C_{13}-$C\underline{H}_3$), 0.91, 0.82 (other methyl groups).

5-Keto-5,6-secocholest-3-en-6-oic acid (CCLXIV)

3β-Acetoxy-5,6-secocholestan-5-keto-6-oic acid (1 g) was dissolved in methanol (100 ml) and to this, sodium bicarbonate (1 g) was added. The reaction mixture was allowed to stand at

room temperature for 27 hours with occasional shaking. Towards the end of the reaction period, most of the added bicarbonate had gone into the solution. The reaction mixture was diluted with water (300 ml), acidified (HCl) and extracted with ether. The ethereal solution was washed with water and dried over anhydrous sodium sulphate. It provided 5-keto-5,6-secocholest-3-en-6-oic acid (CCLXIV) (0.87 g) as a non crystallizable oil[118]; $\nu_{max.}$ 3400-3200 br(COO<u>H</u>), 1710 s(<u>CO</u>OH), 1685 cm^{-1} (C=C-C=O).

<u>Methyl 5-keto-5,6-secocholest-3-en-6-oate (CCCXLVIII)</u>

A solution of 5-keto-5,6-secocholest-3-en-6-oic (CCLXIV) acid (1 g) in the cold ether (20 ml) was treated with an excess of an ethereal solution of diazomethane. After usual work up of the reaction mixture, the methyl ester (CCCXLVIII) (0.8 g) was obtained as homogeneous oil[118]; $\nu_{max.}$ 3040 w(C=C-<u>H</u>), 1735 ($COOCH_3$), 1675 s(C=C-C=O), 1615 (C=C) and 1165 cm^{-1} (methyl ester); δ (60 MHz), 6.75 m(1H, C_3-<u>H</u>), 5.8 d(1H, C_4-<u>H</u>), 3.57 s(3H, $COOC\underline{H}_3$), 2.8 m(2H, C_7-2<u>H</u>), 1.07 s(3H, C_{10}-$C\underline{H}_3$), 0.88, 0.8, and 0.66 (other methyl groups).

<u>Reaction of methyl 5-keto-5,6-secocholest-3-en-6-oate (CCCXLVIII) with an excess of hydrazoic acid : Methyl 5,6-seco-4a-oxo-5-aza-A-homocholest-3-en-6-oate (CCCLII)</u>

To a solution of hydrazoic acid (20 ml) [prepared as

described earlier] was added boron trifluoride-etherate (1 ml) in the cold. A solution of the ester (CCCXLVIII) (1 g) benzene (20 ml) was then added in about 5 hours and the reaction mixture was kept at room temperature for 3 days. Benzene was removed by distillation under reduced pressure and the residue was dissolved in ether. The ethereal solution was washed with water, $NaHCO_3$ (10%) and again with water and dried over anhydrous sodium sulphate. Evaporation of the solvent furnished (CCCLII) as an oil which was chromatographed over silica gel (20 g). Elution with light petroleum-ether (9:1) afforded (CCCLII) (400 mg), m.p. 184°; $\nu_{max.}$ 3400, 3140 (NH), 1740 ($\underline{COO}CH_3$), 1675 (CONH), 1640 cm^{-1} (C=C); δ 7.15 br(1H, CONH; exchangeable with deuterium), 5.7 br,m(1H, C_3-$\underline{H}$), 4.7 br,m(1H, C_4-$\underline{H}$), 3.5 s (3H, $COOC\underline{H}_3$), 2.5 br,m(4H, C_2-$\underline{H}_2$ and C_7-$\underline{H}_2$), 1.2 s(3H, C_{10}-$C\underline{H}_3$), 0.9, 0.8 and 0.6 (other methyl groups).

Analysis Found : C, 75.41; H, 10.60; N, 3.11

$C_{28}H_{47}NO_3$ requires : C, 75.45; H, 10.63; N, 3.14%.

Baeyer-Villiger oxidation of 6ξ-acetylcholest-4-en-3-one(CCCXXIV): Methyl 4α,5-epoxy-cholestan-3-oxo-6ξ-carboxylate (CCCLVII) and methyl 3-oxo-4aα,5-epoxy-A-homo-5α-cholestan-4-oxa-6ξ-carboxylate (CCCLV)

To a solution of the ketone (CCCXXIV) (3 g) in chloroform (25 ml), a chloroform solution of perbenzoic acid (2.5 mole equiv.

and a few crystals of p-toluenesulphonic acid was added and the reaction mixture was allowed to stand at room temperature for 96 hours. The progress of the reaction was monitored by t.l.c. The reaction mixture was poured into ice-cooled water and extracted with ether. The ethereal layer was washed with sodium bicarbonate solution (5%) and water and dried over anhydrous sodium sulphate. Removal of the solvent furnished an oil (2.4 g) which was chromatographed over silica gel (60 g). Each fraction of 25 ml was collected. Elution with light petroleum-ether (15:1) provided the epoxide (CCCLVII) as an oil 'B$_1$' (400 mg) which failed to crystallize ; $\nu_{max.}$ 1740 ($COOCH_3$), 1705 (C=O), 910 cm^{-1} (epoxide); δ 3.8 s(1H, $C_4\beta$-H), 3.6 s(3H, CH_3O-CO-), 3.3 m(1H, $C_6\xi$-H, $W_{\frac{1}{2}}$ 9 Hz), 2.03 br,m(2H, C_2-H_2), 1.2, 1.16, 0.95, 0.85 and 0.71 (other methyl groups).

Analysis Found : C, 75.92; H, 10.09

$C_{29}H_{46}O_4$ requires : C, 75.93; H, 10.11%.

Further elution with light petroleum-ether (10:1) furnished the epoxy lactone (CCCLV) as a non crystallizable oil 'B$_2$' (500 mg); $\nu_{max.}$ 1750 br($COOCH_3$ and epoxy lactone moiety), 910 cm^{-1} (epoxide); δ 4.0 s(1H, $C_{4a}\beta$-H), 3.5 s(3H, -COCH_3), 3.1 br,m(1H, $C_6\xi$-H, $W_{\frac{1}{2}}$ 8 Hz), 2.56 br,m(2H, C_2-H_2), 1.38, 1.28, 1.2, 0.8 and 0.7 (other methyl groups).

Analysis Found : C, 73.35; H, 9.72

$C_{29}H_{46}O_5$ requires : C, 73.37; H, 9.76%.

Reaction of 2,6-dibormocholesta-1,4,6-trien-3-one (CCCXXXVI) with perbenzoic acid : 6,7α-Oxido-2,6-dibromocholesta-1,4-dien-3-one (CCCLXII-a)

To a solution of the ketone (CCCXXXVI) (2 g) in chloroform (10 ml), a chloroform solution of perbenzoic acid (2.5 mole equiv.) and a few crystals of p-toluenesulphonic acid was added and the reaction mixture was allowed to stand at room temperature for 96 hours. The progress of the reaction was monitored by t.l.c. The reaction mixture was poured into ice-cooled water and extracted with ether. The ethereal layer was washed with sodium bicarbonate solution (5%) and water and dried over anhydrous sodium sulphate. Removal of the solvent gave an oil which was crystallized from methanol to give the epoxy ketone (CCCLXII-a) (800 mg), m.p. 145°; $\nu_{max.}$ 1685 (C=C-C=O), 1610 (C=C), 910 (epoxide), 760 cm^{-1} (C-Br); δ 7.1 s(1H, C_1-H), 6.75 s(1H, C_4-H), 3.48 (1H, $C_7\beta$-H), 1.3 s(3H, C_{10}-CH_3), 0.9, 0.8 and 0.75 (other methyl groups).

Analysis Found : C, 58.46; H, 6.85

$C_{27}H_{38}O_2Br_2$ requires : C, 58.49; H, 6.90%.

MASS SPECTRAL STUDIES ON STEROIDAL NITROOLEFINS

Preparations

6-Nitrocholest-5-ene (CCCLXXXI)

A suspension of finely powdered cholest-5-ene (CCCVIII) (6 g) in glacial acetic acid (50 ml) was vigorously stirred at room temperature and treated with nitric acid (15 ml; d, 1.5), followed by addition of sodium nitrite (3 g) over a period of one hour. The reaction mixture was poured into cold water and the yellow solid mass thus obtained was extracted with ether. The ethereal layer was washed successively with water, sodium bicarbonate solution (5%) and again with water and dried over anhydrous sodium sulphate. Removal of the solvent provided the desired compound as an oil which was crystallized from ethanol to give 6-nitrocholest-5-ene as leaflets (4.5 g), m.p. 119-120° (lit.[142] m.p. 120-121°).

3β-Chloro-6-nitrocholest-5-ene (CCCLXXXII)

To a well stirred mixture of 3β-chlorocholest-5-ene (CCCIX) (12 g), glacial acetic acid (80 ml) and nitric acid (25 ml; d, 1.5) at temperature below 20°, was added sodium nitrite (3 g) gradually over a period of two hours. After complete addition of sodium nitrite, the mixture was stirred for about one hour. Ice-cooled water was added and the yellowish solid

thus obtained was filtered under suction and air dried. Recrystallization from methanol gave the desired 3β-chloro-6-nitro--cholest-5-ene (CCCLXXXII) as needles (8.3 g), m.p. 151-152° (lit.[143] m.p. 153°).

3β-Acetoxy-6-nitrocholest-5-ene (CCCLXXXIII)

3β-Acetoxycholest-5-ene (CCCX) (5 g) was covered with nitric acid (100 ml; d, 1.42) and fuming nitric acid (25 ml; d, 1.52) was added to it. Sodium nitrite (5 g) was added to the suspension gradually over a period of one hour with continuous stirring. Slight external cooling was also affected during the course of the reaction, and the stirring was continued for additional two hours. The mixture was diluted with an excess ofice-cooled water when a yellow spongy mass separated on the surface and a green coloured solution was obtained. The whole mass was extracted with ether. The ethereal solution was washed successively with water, sodium bicarbonate solution (5%) and again with water and dried over anhydrous sodium sulphate. Evaporation of the solvent provided the nitro compound (CCCLXXXIII) as an oil which was crystallized from methanol (3.5 g), m.p. 104° (lit.[138] m.p. 102-104°).

The mass spectra were measured on a AEI MS-9 and JMS-D300 mass spectrometers at 70 eV using a direct insertion technique at a source temperature of about 200° C.

The values (m/z) of the fragment ions from various nitro-olefins are tabulated below. The values in parentheses are the relative abundance (%) of the peaks with respect to the base peak taken as 100%.

6-Nitrocholest-5-ene (CCCLXXXI)

M^+ 415(68.9; $C_{27}H_{45}NO_2$), 400(15.5), 399(24.4), 398(77.7), 397(8.8), 385(13.3), 383(5.5), 382(8.8), 372(17.7), 371(22.2), 370(44.4), 369(68.9), 368(40.0), 367(11.1), 356(8.8), 355(11.1), 353(8.8), 342(4.4), 330(4.4), 328(4.4), 316(4.4), 314(4.4), 302(4.4), 300(4.4), 286(17.7), 274(6.6), 272(11.1), 260(6.6), 258(13.3), 255(13.3), 247(15.5), 244(17.7), 230(13.3), 218(15.5), 215(15.5), 213(8.8), 175(17.7), 161(31.1), 159(26.6), 149(20.0), 147(28.8), 145(22.2), 138(17.7), 135(24.4), 133(20.0), 131(15.5), 123(22.2), 121(33.3), 119(22.2), 117(11.1), 111(31.1), 109(40.0), 107(37.7), 105(35.5), 97(26.6), 95(88.9), 93(55.5), 91(37.7), 83(44.4), 81(68.9), 79(40.0), 77(17.7), 74(17.7), 71(48.9), 69(66.6), 67(48.9), 59(53.3), 57(88.9) and 55(100).

3β-Chloro-6-nitrocholest-5-ene (CCCLXXXII)

M^+ 449/451 (88.5/30.0; $C_{27}H_{44}NO_2Cl$), 434/436 (34.2/5.7), 432/434 (55.7/34.2), 419/421 (21.4/7.1), 416 (10.0), 414(28.5), 413(15.7), 403/405(57.1/21.4), 398(4.3), 396(14.3), 383(21.4), 370(7.1), 368(14.3), 356(8.5), 355(5.7), 336/338(8.5/2.8),

329(8.5), 320/322(5.7/2.1), 308/310(7.1/2.8), 278/280(21.4/8.5), 209/211(12.8/4.3), 195(15.7), 193(12.8), 183(7.1), 181(5.7), 172 (14.2), 161(8.5), 159(15.7), 157(14.3), 147(12.8), 145(14.3), 143(10.0), 135(20.0), 133(14.3), 131(10.0), 123(10.0), 121(14.3), 119(17.1), 109(24.3), 107(28.5), 105(22.8), 97(18.5), 95(57.1), 91(32.8), 83(34.2), 81(60.0), 79(31.4), 77(14.3), 71(44.3), 69(65.7), 67(35.7), 57(91.4), 55(100).

3β-Acetoxy-6-nitrocholest-5-ene (CCCLXXXIII)

M^+ 473($C_{29}H_{47}NO_4$), 413(23.4), 398(11.1), 396(20.0), 385(17.7), 384(40.0), 383(48.9), 370(22.2), 368(35.5), 366(13.3), 365(8.8), 356(20.0), 342(6.6), 329(24.4), 314(6.6), 300(6.6), 286(4.4), 284(4.4), 282(4.4), 272(4.4), 261(4.4), 175(13.3), 173(13.3), 171(6.6), 166(11.1), 163(8.8), 161(11.1), 159(22.2), 157(17.7), 149(17.7), 147(20.0), 145(24.4), 143(17.7), 137(13.3), 135(35.5), 133(22.2), 131(15.5), 129(11.1), 123(22.2), 121(33.3), 119(31.1), 117(17.7), 111(15.5), 109(42.2), 107(62.2), 105(35.5), 97(28.8), 95(86.6), 93(44.4), 91(42.2), 85(13.3), 83(42.2), 81(91.1), 79(40.0), 77(17.7), 71(51.1), 69(88.9), 67(44.4), 60(28.8), 57(100), 55(95.5).

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